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Extracorporeal Shockwave Lithotripsy using Ultrasonic Imaging: Urologists' Experience

E. A. KIELY, P. C. RYAN, T. E. D. McDERMOTT and M. R. BUTLER

National Stone Centre, Meath Hospital, Dublin, Ireland

Summary—The EDAP LT.01 is a second generation shockwave lithotripter which employs ultrasound imaging and piezoelectric shockwave generation. We describe the first 12 months of its use in the treatment of urinary calculi by urologists with no previous practical experience of ultrasonography. A total of 406 calculi (359 renal and 47 ureteric) in 317 patients were treated. Analgesia or sedation was not routinely used and 59% of all treatments were performed as out-patient procedures. The clearance rate of renal calculi smaller than 1 cm was 81%, while that of calculi larger than 3 cm was 80% (mean clearance 77.5%). Lithotripsy of ureteric calculi following retrograde manipulation to a renal site resulted in 94.4% clearance compared with 39% for those treated at a ureteric site; 93% of 684 lithotripsy treatments were either painless or caused only mild pain. Our experience with imaging and treating urinary calculi with the EDAP LT.01 lithotripter has been excellent. Patients are treated effectively and inexpensively as out-patients without analgesia or sedation.

Since the development of first generation Dornier lithotripters, which employed fluoroscopy for calculus imaging and electrohydraulic shockwaves for disintegration, more recent designs have used alternative modalities of visualisation and lithotripsy. The EDAP LT.01 (EDAP International Co., Croissy Beaubourg 77200, France) is a second generation shockwave lithotripter in which calculi are imaged by a standard 5 MHz diagnostic ultrasound sector scanner; shockwaves are produced by an array of 340 ceramic piezoelectric elements mounted on a concave dish 40 cm in diameter. The ultrasound probe and the piezoelectric shockwave generating elements are covered by a water-filled pouch and located within the same mobile unit referred to as the processing head. The rubber pouch is coupled to the patient using ultrasound transmission jelly.

The EDAP LT.01 has several advantages over the earlier first generation lithotripters, the principal one being that treatment is either pain-free or entails only mild discomfort. This allows patients to be treated on an out-patient basis without sedation. In contrast, earlier lithotripters required both general anaesthesia and hospitalisation. This advantage also means that repeated treatments for large calculi can be easily administered without the need for repeated admissions. The reasons why EDAP LT.01 lithotripsy is pain-free are: (1) the energy focus is small and therefore tends to concentrate shockwaves on the target calculus without traumatising the surrounding tissues and (2) the wide aperture of the concave dish means that energy intensity at skin level is not sufficient to cause pain. A further advantage is the lack of exposure of either patients or staff to X-rays, in contrast to lithotripters which employ fluoroscopic imaging. Ultrasonic imaging also means that radiolucent calculi in both the urinary and the biliary tract can be visualised and treated. Furthermore, ECG gating is not required during treatment.

This lithotripter is relatively cost-effective, with a capital outlay of £600,000. It is inexpensive to run as it requires only a standard electrical power source and the elements that produce the shockwaves do not require routine replacement during and after treatment, as is the case with spark-gap

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Read at the 44th Annual Meeting of the British Association of Urological Surgeons in Buxton, June 1988

generated lithotripters. Since the energy source is divided between 340 units rather than 1 spark-gap source, wear and tear on each power unit is minimal and this results in low maintenance costs. Finally, the EDAP LT.01 design allows considerable versatility in the type of shockwave treatment that can be administered. The power can be increased in 14 steps from 1–100%. In addition, shockwaves can be delivered at frequencies which can be varied from 1.25 to 160 shocks per second. The latter facility allows treatment to be administered over short periods of time.

Piezoelectric shockwaves differ qualitatively from those produced by other types of lithotripters. This fact, together with the shockwave frequency alterations that may be made on the EDAP LT.01 even during a single treatment session, make the quoting of the total number of shockwaves per treatment meaningless when compared with non-piezoelectric lithotripters.

A disadvantage of the EDAP LT.01 lithotripter is the difficulty for non-radiological personnel in learning to use ultrasound for the imaging of calculi. It was expected that major difficulties would arise in patients who were obese, who had scarred kidneys or who had had previous renal surgery.

In May 1987 the Urological Department in this hospital became one of the first in Europe, outside France, to acquire the EDAP LT.01 lithotripter. We report our experience during the initial 12 months of its use by personnel with no previous training in lithotripsy or ultrasonography.

Patients and Methods

In a series of 317 patients (181 male and 136 female), 406 calculi have been treated during the first 12 months. The mean age of the patients was 46.4 years (range 3–87); 359 calculi were intrarenal and 47 were ureteric. The range of stone size is shown in the Table. In 97% of patients neither sedation nor analgesia was required. A pre-treatment plain abdominal X-ray was obtained where appropriate. Lithotripsy was carried out by urologists or urological trainees.

Initial ultrasound imaging is performed using the 5 MHz hand-held probe which is standard with the EDAP LT.01. The orientation and angulation of the probe producing the best image of the calculus are noted and recorded using the memory function of the ultrasound monitor. This facilitates subsequent imaging using the ultrasound probe within the processing head.

As treatment progresses, the stone image and acoustic shadow may enlarge and become less distinct. However, these changes are quite subtle and assessment of stone disintegration using real-time imaging is unreliable. For this reason, standard treatment dosages related to stone size have been derived from experience of using the EDAP LT.01. Thus treatment lasting 40 min (100% power; frequency 2.5 Hz, *i.e.* 6000 shocks) is appropriate for a 1-cm stone.

The power of the shockwaves is gradually increased over the first 5 min. This allows the patient to relax and improves treatment tolerance. If marked discomfort is experienced the power and/or frequency of the shockwaves is reduced. On the rare occasion that this fails to bring relief, an intravenous opiate analgesic is administered. A plain X-ray is obtained immediately after treatment and if sub-total disintegration of the stone is suspected, this X-ray is repeated 3 weeks later before deciding on the need for repeat ESWL.

During the initial 12 months, 59% of all ESWL was given on an out-patient basis; 8.1% of patients required admission for 1 day and 23.8% required admission for more than 3 days. The longer admission periods were required where adjuvant therapies were combined with ESWL, or to allow treatment of unrelated conditions.

Of the 32 calculi >2 cm in diameter, 8 were treated by a combination of ESWL and percutaneous nephrolithotomy; 3 of these were renal staghorn calculi and 5 were large pelvic stones. The remaining 24 large renal calculi (including 16 staghorn) were treated by ESWL monotherapy; 27 of the 47 ureteric calculi were treated by ESWL following retrograde manipulation to an intrarenal site (push/ESWL) by either ureteroscopy or the passage of a ureteric catheter.

Results

The mean time required for stone imaging was 8.9 min (range 1–30) and the mean treatment time was 38.9 min (range 8–63). Further details of treatment are demonstrated in the Table.

The mean period of follow-up was 3.2 months. Complete clearance (100%) of a calculus means that no evidence of that calculus is seen on a follow-up X-ray. Renal calculi had a mean clearance rate of 79.9%. Calculi <1 cm in diameter had a clearance rate of 81.8%, while those >3 cm had a mean clearance of 80%. The percentage of kidneys which were free of these stones at 3 months was 74 and 49% respectively. The mean number of lithotripsy treatments required was directly related to

Table Details of Lithotripsy Treatment

Site	*Calculus size (cm)*	*Number*	*Mean number ESWL sessions (range)*	*Mean clearance (%)*	*Stone free at 3/12 (%)*
Renal	0–1	228	1.33 (1–3)	81	74
	1–2	99	1.94 (1–5)	76.2	61
	2–3	15	2.92 (1–8)	86.7	64
	3	17	3.96 (2–11)	80	49
Ureteric					
(*in situ*)	—	20	1.56 (1–3)	39	*
(Push/ESWL)	—	27	1.18 (1–3)	94.4	*

*Failures treated by endourology

stone size: 1.33 sessions were required for stones <1 cm and 3.96 for those >3 cm. Of the 16 staghorn calculi treated by ESWL monotherapy the clearance rate in 10 was over 90%; in 1 it was 50% and in 5 less than 50%. Each of the 5 pelvic calculi treated by a combination of ESWL and percutaneous nephrolithotomy was cleared completely. The mean clearance of 3 staghorn calculi treated by these combined methods was 97%.

Twenty-seven of the 47 ureteric calculi had lithotripsy following retrograde manipulation of the calculus (push/ESWL). The clearance rate for these calculi was 94.4%. Of the remaining 20 ureteric calculi which were treated *in situ* by ESWL only 6 were cleared completely.

Of 684 lithotripsy treatments, 430 (62.9%) were completely painless, 205 (29.9%) caused mild pain, 43 (6.3%) resulted in pain described as bearable and 6 (0.9%) were aborted because of pain. Discomfort during ESWL necessitated a reduction from 100% power in 74 procedures and a reduction in frequency from 2.5 Hz in 72. An opiate analgesic was required for only 20 treatments.

The only complication was ureteric obstruction. This followed 6 treatments (0.9%) and resulted from a stone fragment in 4 cases and a "steinstrasse' in 2. Two of the stones treated were partial staghorns, 2 were large pelvic calculi and 2 were caliceal stones. None of these treatments was performed with a ureteric stent *in situ*. Three of these patients were managed by ureteroscopic manipulation, 2 were successfully treated conservatively and the remaining patient presented to a District General Hospital and received a ureterolithotomy.

Discussion

As can be gauged from these results, our experience with the EDAP LT.01 lithotripter has been satisfactory and initial fears that lack of experience in ultrasonography would be a major disadvantage have proved groundless. Following an initiation period of 3 to 4 weeks, the novice ultrasonographer's ability to use the EDAP LT.01 was quite adequate. A period of practice using a "phantom imager" is helpful but is no substitute for *in vivo* scanning. In all but the more obese subjects, the renal outline is easily recognisable and subsequent intrarenal stone localisation is simple. The resolution of the scanning probe allows even the smaller intrarenal calculus to be visualised. The manoeuvrability of the processing head allows the optimal image to be obtained without moving the patient. The mean imaging time of 8.9 min was most acceptable. The major scanning difficulties were encountered in the obese, those who had had previous renal surgery and in those with ureteric calculi. We found that in such patients, scanning and treatment in the lateral position was usually more satisfactory.

Our experience with lithotripsy of calculi within the ureter has been less successful. Only 6 of 20 such stones have been cleared, while 25 of the 27 ureteric calculi manipulated back to the kidney were successfully treated. Ureteric calculus manipulation in our unit is frequently performed under local anaesthesia at cystoscopy. A size 4 olive-tipped ureteric catheter is used to instill 10 ml of 1% lignocaine into the ureter. A4F double J ureteric catheter is then inserted. We find this an efficient and convenient method of ureteric stone manipulation as the EDAP LT.01 treatment table is adaptable for all urological procedures.

Stones <2 cm constitute the model size for extracorporeal lithotripsy (Drach *et al.*, 1986; Vallancien *et al.*, 1988). While 91% of calculi in our series were within this range, no special selection process was employed whereby the larger stones were excluded. Our experience with these larger stones supports the view that where complete stone clearance is the aim, the combination of ESWL with a prior reduction in a stone load by percutaneous nephrolithotomy is recommended (Webb, 1986). However, by the use of ESWL alone we achieved at least 90% clearance in 10 of 16 staghorn calculi. Although multiple ESWL sessions were required in these cases, treatment was pain-free and administered on an out-patient basis. This suggests that if the patient and urologist are prepared to invest the time required, ESWL monotherapy is an acceptable treatment option for staghorn calculi using the EDAP LT.01.

The performance of the EDAP LT.01 regarding pain tolerance is worthy of particular emphasis. After an initial brief period where parenteral analgesia was frequently given, this practice is now rare. This change is probably due in part to the improved targeting of shockwaves, since any pain that is experienced seems to occur when the energy focus strays off the calculus. The result is that patients are now treated on a true out-patient basis, arriving and leaving the lithotripter centre completely alert and ambulant. This contrasts with earlier generation machines where admission and general anaesthesia were required, and also with other more recent lithotripters where intravenous analgesia or sedation necessitated day-case admission and assisted transport after treatment.

In the early phase of our experience, the use of ureteric stents during treatment of the larger stones (Sofras *et al.*, 1988) was not fully appreciated. Four of our 6 cases of ureteric obstruction following ESWL would have been avoided had we used ureteric stenting (as is now our practice) for stones >3 cm in diameter.

Treatment and maintenance costs with the EDAP LT.01 have been negligible. Over the 12-month period the only component requiring replacement has been the rubber membrane covering the processing head. These membranes are inexpensive and can be replaced within 1 h. Minimal staff requirements, no routine change of parts (*e.g.* spark-gap electrode) and out-patient treatment are characteristics which reduce treatment costs. Our favourable experience with the EDAP LT.01 indicates that an extracorporeal shockwave lithotripter with ultrasound stone localisation can be operated effectively by non-radiological personnel.

The machine is inexpensive to purchase, maintain and use and introduces a new dimension in non-invasive stone management: efficient and painless out-patient extracorporeal lithotripsy without analgesia or sedation.

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Extracorporeal Piezoelectric Lithotripsy for all Renal Stones: Effectiveness and Limitations

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Summary—An unselected group of patients with renal stones was treated with extracorporeal piezoelectric lithotripsy (EPL) monotherapy. The results showed that this minimally invasive treatment was very effective for patients with stones smaller than 20 mm. After a minimum follow-up of 1 month, 65% of these patients were stone-free and 22% of the remainder had only small fragments. Patients with larger stones (20 mm or larger) required multiple treatment sessions (mean 5.8) and had less favourable results. One month or more after treatment, only 46% of these patients were free of stone and 21% required secondary operative procedures for obstructing ureteric fragments. Most of these patients are better treated initially by percutaneous nephrolithotomy.

The introduction of extracorporeal shock wave lithotripsy (ESWL) by Chaussy *et al.* (1980) revolutionised the treatment of upper urinary tract stone disease. Shock wave lithotripsy is now the treatment of choice for over 80% of upper tract stones (Eisenberger *et al.*, 1985; Webb *et al.*, 1986). The original lithotriptors (Dornier HM1, HM2 and HM3) had shortcomings. The electrohydraulic shock wave was painful, making anaesthesia essential, and the fluoroscopic stone localisation system expensive and cumbersome. This led to the development of several "second generation" machines. The Scottish Lithotriptor Centre was established in September 1987. The service is based in Edinburgh and uses a Wolf Piezolith 2300. This features an ultrasound stone localisation system and a piezoelectric shock wave generator. To evaluate the effectiveness of the machine we treated an unselected group of patients with renal stones with extracorporeal piezoelectric lithotripsy monotherapy. All patients were accepted for treatment provided there was no evidence of an obstructing lesion distal to the stone which might impede elimination of the stone particles. We present our experience in treating stones in 400 kidneys in 384 patients.

Patients and Methods

The Wolf Piezolith 2300 is shown schematically in Figure 1. Coaxial ultrasound is used for stone localisation. A second probe, mounted at a different angle, is available should acoustic shadowing from a rib obscure the stone. Over 2000 piezoceramic crystals mounted on a section of spherical dish generate the shock wave. This focusing dish has a wide aperture (50 cm), resulting in a wide, painless zone of shock wave entry into the body and a small shock wave focus (4 mm in diameter × 9 mm in length). The shock waves are transmitted by degassed water from the dish to the patient's body which is partially immersed in the small water bath. The shock wave focus is placed on the stone by moving the focusing dish.

Between September 1987 and August 1988, stones in 400 kidneys in 384 patients were treated (Table 1). Most patients were referred from centres in Scotland outside the Edinburgh area. The referring urologist managed any post-treatment problems and conducted the follow-up of these "distant" patients.

The location and size of the stones are shown in Table 1. Only 21% were in the renal pelvis. There were 23 patients with complete staghorn stones; 38% of the stones were 20 mm or more in maximum

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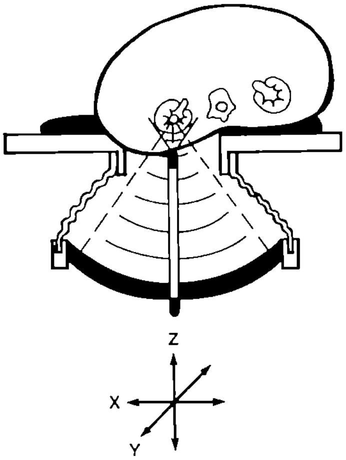

Fig. 1 Schematic representation of Wolf Piezolith showing shock wave generator dish, ultrasound probe, water bath and patient position.

diameter. Preliminary procedures are listed in Table 2. Our initial policy was not to perform preliminary ureteric stenting or percutaneous debulking in patients with large stones. However, some patients underwent these procedures prior to referral.

Immediately after treatment a plain radiograph was obtained to assess the adequacy of fragmentation. Generally, if fragments larger than 4 mm remained, re-treatment was arranged. Otherwise plain radiographs were requested at 10 days, 1 and 3 months after treatment.

Table 1 Details of 384 Patients

Stone location (n=400)	*No*	*(%)*
Upper calix	30	(7)
Middle calix	21	(5)
Lower calix	116	(29)
Renal pelvis	86	(21)
Upper ureter/PUJ	38	(10)
Mid ureter	11	(3)
Lower ureter	7	(2)
Multiple sites	41	(10)
Partial staghorn	27	(7)
Complete staghorn	23	(6)

Stone size (mm) (n=400)*	*No*	*(%)*
1–9	115	(29)
10–19	134	(33)
20–29	70	(18)
30	81	(20)

*Largest diameter on plain radiograph.

Age (years)	Mean 50.7 (range 3–87)
Sex	Female male=1:1.2
Referral source	Local: distant=1 1 9

Table 2 Preliminary Procedures in 48 Patients

	No
Retrograde push	32
Ureteric stent	9
Percutaneous nephrolithotomy	8
Percutaneous nephrostomy	5

Results

Treatment was given solely on an out-patient basis in 69% of patients and was given without anaesthesia or sedation to all except two 3-year-old children who required general anaesthesia. Two 4-year-old children were successfully treated without sedation or anaesthesia. The average treatment session lasted about 40 min and consisted of 2600 shocks (range 1000–6000).

The results are shown in Table 3 and are influenced by a median follow-up period (interval between the most recent treatment session and follow-up radiograph) of only 23 days. Follow-up information 1 month or more after treatment was available in almost half of the patients. Of these patients, 65% with stones <20 mm (small stones) and 46% with stones of 20 mm or more (large stones) were stone-free. If all 400 kidneys are included for analysis, irrespective of the follow-up interval, 55% of patients with small stones and 30% of those with large stones were stone-free. To achieve this result, patients with small stones received an average of 1.7 treatment sessions and

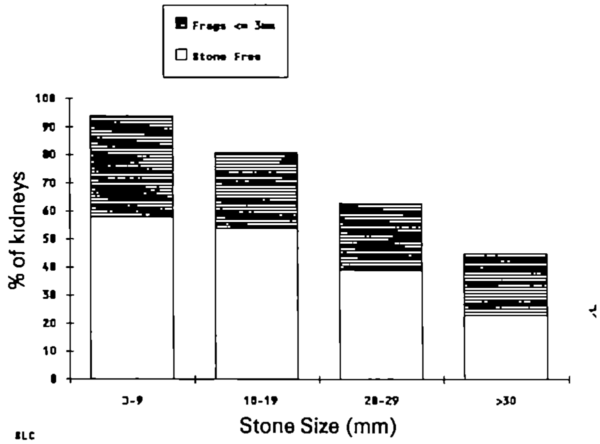

Fig. 2 Influence of stone size on result.

Table 3 Results

	Stone <20 mm	*Stone 20 mm or more*
No. of kidneys	249	151
Median follow-up (days)	22	26
No. of kidneys with follow-up of 30 or more days	101	63
Fragmentation rate (%)	93	96
Stone-free after minimum follow-up of 30 days (%)	65	46
Stone-free (overall) (%)	55	30
Stone-free or fragments <4 mm (%)	87	53
Mean treatment sessions/kidney (range)	1.7 (1–10)	5.8 (1–24)
Mean no. of shocks/kidney (range)	5100 (500–26,000)	15,700 (1900–87,500)

those with larger stones received an average of 5.8 sessions. The influence of initial stone size on the result is examined further in Figure 2. Note that most patients with original stones <20 mm are either free of stone or have only small residual fragments. The results for larger stones were much less encouraging, despite multiple treatment sessions. Many of these patients have now undergone percutaneous nephrolithotomy and are currently receiving EPL to residual fragments.

Initial treatment with EPL failed in 37 patients. The most common reasons were failure to image ureteric stones with ultrasound, or little or no progress in pulverisation of large or hard renal stones. The endoscopic techniques listed in Table 4 were used in the successful treatment of these patients, who were included in the analysis of results. After ureteric stones were dislodged back to the kidney or large stones were debulked percutaneously, most patients received further EPL treatment.

Complications of treatment are shown in Table 5A. There were no cases of pancreatitis or of perirenal haematoma. Sepsis requiring treatment with intravenous antibiotics occurred in 16 patients (4%), most often in those with staghorn stones. Since the majority of patients underwent post-treatment follow-up in other centres, we have no accurate data on the incidence of post-treatment colic. Secondary procedures for obstructing ureteric stone fragments were required in 11% of patients (Table 5B); 15 patients had obstructing fragments successfully treated with EPL alone; the remaining 31 (8%) required 44 procedures under anaesthesia.

Stone size influenced the risk of complications from an obstructing stone fragment. Secondary

Table 4 Procedures Required for Stones Failing Initial EPL Treatment

		No
Retrograde push + EPL		6
Ureteroscopic stone extraction		1
Ureteric meatotomy		1
Reasons for percutaneous stone extraction:		
Large stone size	17	29
Dense/laminated stone	5	
Rib shielding	3	
Cystine stone	1	
Impacted upper ureteric stone	3	
Total		37

Table 5 Complications

(A) Overall	*No.*	*(%)*
Perirenal haematoma	0	
Pancreatitis	0	
Sepsis (temp. >38.5°C)	16	(4)
Obstructing ureteric fragments	46	(11)
Nephrectomy (perinephric abscess)	2	(1.5)
Nephrectomy (pyonephrosis)	2	(1)
Ureteric stricture (ureteroscopy)	3	(1)

(B) Procedures for obstructing ureteric stone fragments	*Stone size*			
	20 mm		*20 mm*	
	*(n=249)**		*(n=151)†*	
EPL alone	3	(1%)	12	(8%)
Retrograde push + EPL	2	(1)	4	(3)
Ureteroscopic extraction	7	(3)	15	(10)
Percutaneous extraction	1	(0.5)	9	(6)
Basket extraction	2	(1)	0	
Percutaneous nephrostomy	1	(0.5)	1	(1)

* Complications occurred in 14 patients (6%).
† Complications occurred in 32 patients (21%)

procedures were performed in 32 patients (21%) with stones >20 mm compared with 14 patients (6%) with smaller stones. Four patients underwent nephrectomy; 2 patients with branched struvite stones developed a perinephric abscess after undergoing EPL (possibly an unrelated event); 2 patients with asymptomatic ureteric stone fragments developed a pyonephrosis and both ultimately required nephrectomy for a non-functioning kidney. Three patients had ureteroscopic procedures complicated by ureteric stricture formation; 1 was managed simply by endoscopic dilatation and another required reimplantation. The third stricture complicated antegrade ureteroscopy and awaits management.

Discussion

These results show that renal stones <20 mm can be effectively treated in a non-invasive way with the Wolf Piezolith. Treatment was given without anaesthesia or sedation in all patients except two 3-year-old children. Shock wave pressure at the focus (1000 bar) is similar to that of the Dornier HM1, 2 and 3 models, but the wider aperture of the focusing dish results in a wide, pain-free zone of shock wave entry into the body (Wurster *et al.*, 1987). Some patients with stones close to the posterior body wall (children, slim patients and those who have undergone previous open renal surgery) feel some discomfort during treatment. Reducing the shock wave intensity remedies the problem with little effect on the efficacy of treatment. Periosteal pain may be experienced by patients with stones adjacent to a lower rib, but repositioning usually solves the problem. Lithotripsy without anaesthesia lowers staffing costs, allows most patients to be treated as out-patients and enables great flexibility in treatment scheduling.

The Wolf Piezolith uses coaxial ultrasonography for stone localisation. None of the operators had previous experience in renal ultrasonography but after some weeks' practice almost all renal stones were readily localised. This is reflected in a stone fragmentation rate of 94%. A radiologist experienced in real-time ultrasonography reviewed both the video recordings and the plain radiographs of 100 of our treatments and concluded that the fragmentation rate was 92%. Failed treatment was usually due to localisation failure (Reid *et al.*, unpublished material). Renal stones in obese patients and in those with a history of previous open renal surgery were sometimes difficult to image. Perirenal scarring is seen ultrasonographically as multiple bright echoes which obscure the renal image and also cause some attenuation of the shock wave. Ureteric stones are more difficult to image with ultrasound. If the upper ureter is dilated, the obstructing stone can usually be localised. Of 49 stones in the pelviureteric junction and upper and mid ureters, 14 were successfully localised and treated *in situ*. The remainder required endoscopic manipulation (usually retrograde dislodgement). Using the bladder as an acoustic window, 5 distal ureteric stones were successfully treated *in situ*. These stones were all either in the intramural or distal 2 cm of the juxta-vesical ureter.

Ultrasound stone localisation has advantages over fluoroscopic localisation in that the position of the stone can be constantly monitored, small and radiolucent stones are readily imaged, there is no irradiation to the patient or staff during treatment, and lithotriptor cost is reduced. The main disadvantage of ultrasound is that stones in the upper and mid ureters may be more difficult to locate and often require preliminary dislodgement. Clinical experience, however, suggests that shock wave fragmentation of ureteric stones *in situ* is often ineffective because of the absence of an adequate fluid-filled space around the stone (Mueller *et al.*, 1986). In practice, the inability to treat some ureteric stones *in situ* may be a minor disadvantage.

Treatment of patients with stones <20 mm with EPL was very effective. A stone-free rate of 65% at 1 month or longer for these patients is less than the rate reported in some other studies of both first and second generation machines (Chaussy *et al.*, 1984; Wilbert *et al.*, 1987; Marberger *et al.*, 1988). However, almost all of the patients with residual stone have only small particles (3 mm or less) and when the follow-up interval is extended to 3 months an improvement in the stone-free rate is anticipated. Patients with stones <20 mm in diameter required on average 1.7 sessions of treatment, whereas those treated on a first generation machine usually need only one. In practice, retreatment with the Piezolith was readily performed and well accepted by our patients.

Treatment of large renal stones (>20 mm in diameter) with EPL alone is possible but multiple treatment sessions are necessary and the risk of complications from obstructing stone fragments is high. The small focal point of the shock waves enables targeted treatment of specific portions of large stones. Treatment can be performed in planned stages, the pulverised material being eliminated between sessions. We attempted to treat 151 large stones with this technique and a stone-free status was achieved in only 30%. Successful cases included 3 patients with complete staghorn stones, but multiple sessions (21 for 1 patient) were required and the risk of complications from obstructing fragments was 21%. Furthermore, progress was so slow for 17 patients that EPL monotherapy was abandoned and stones were removed by percutaneous nephrolithotomy. Our revised policy, therefore, is to treat most stones >20 mm percutaneously. Any small residual fragments can be treated with EPL. Other centres report a similar experience. Lingeman *et al.* (1987) concluded that for optimal stone-free rates and minimal morbidity, stones >20 mm were best treated by percutaneous nephrolithotomy. Similarly, Eisenberger *et al.* (1985) reported that the critical size above which a stone should be managed percutaneously was 30 mm. Selected large stones can be successfully treated with EPL monotherapy. Analysis of our EPL results for partial staghorn stones shows that most can be successfully treated. Preliminary placement of a ureteric stent may reduce the morbidity of treating large renal stones with shock wave lithotripsy (Zwergal *et al.*, 1987; Libby *et al.*, 1988). We are currently examining this hypothesis in a selected group of patients with large stones.

Of concern were 2 patients who, following EPL treatment, had asymptomatic ureteric obstruction from stone fragments for 2 to 3 weeks, resulting in irreversible renal damage. Our policy is to obtain plain X-rays 1 week and 1 and 3 months after treatment, but sometimes this schedule is not met. If post-obstructive renal damage is to be avoided, good communication between the referring urologist and the lithotriptor centre, and a rigid follow-up protocol are mandatory.

The Wolf Piezolith enables effective, minimally invasive treatment of most renal stones. The treatment does have limitations and for optimal results most large stones should be treated in combination with percutaneous nephrolithotomy.

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Vesicoureteric Reflux and Urinary Calculi in Children

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Summary—We present 5 patients with urinary calculi and vesicoureteric reflux (VUR). In 4 patients the VUR was probably primary and in 1 it was secondary to the calculus disease. The incidence of calculi with reflux is approximately 0.5% whereas the incidence of reflux with calculi is approximately 8%.

Despite the frequent association of urinary infection with vesicoureteric reflux and urinary calculi, the coexistence of VUR and calculi is rare. VUR may be secondary to stone formation, as in vesical calculi (Taneja, 1975), or may predispose to stone formation when associated with anatomical abnormalities of the collecting system (Amar, 1972). However, the occurrence of primary VUR and urinary calculi is rare (Du Preez and Cremin, 1973; Marks, 1974). Five patients are presented who illustrate the spectrum of the relationship between urinary calculi and VUR. The aetiology, management and prognosis of these patients are discussed.

Case Reports

Case 1 A 4-year-old boy presented with several months' history of abdominal pain, proteinuria and failure to thrive (his weight had fallen below the 3rd percentile). There was a past history of proven urinary tract infections which had not been investigated. On presentation he was anaemic (Hb 7 1 g/dl) and in chronic renal failure (urea 13.3 mmol/l, creatinine 115 μmol/l). The right kidney was enlarged and easily palpable. An IVU showed calculi in the right kidney (staghorn) and right ureter, the left kidney was scarred, showing the typical changes of reflux nephropathy. A micturating cystogram confirmed the presence of bilateral Grade IV VUR DTPA scintigraphy estimated the GFR at 25.8 ml/min/kg^2

At operation the right kidney was explored and a perinephric abscess was found and drained. Pyelolithotomy was abandoned. The lower end of the right ureter was exposed and the ureteric stone removed together with pus and debris from the renal pelvis. The ureter was reimplanted. The pus from the perinephric abscess and an MSU showed a heavy growth of *Proteus*. Biochemical analysis of the ureteric stone showed it was of a mixed infective type.

He made a slow and uneventful recovery. He is awaiting further assessment but it is anticipated that he will require a right nephrectomy and a submucosal injection of teflon to control his left Grade IV VUR.

Case 2. A previously fit 4-year-old girl presented as an emergency with fever, bilateral loin pain and dysuria. An MSU showed a heavy growth of *Proteus*. An IVU showed a grossly enlarged non-functioning left kidney. On cystoscopy the left ureteric orifice was oedematous and a left retrograde ureterogram demonstrated a renal calculus. A left nephrectomy was required for a perinephric and renal abscess · the renal pelvis was full of soft calculus material of a mixed infective type She made a rapid recovery. A micturating cystogram performed 9 months, 6 and 10 years later showed persistent VUR into the remaining lower left ureter During this time she had 2 further urinary infections without recurrence of the calculi. The ureteric remnant was eventually excised 10 years after the initial operation. She has remained symptom-free with no complications in the subsequent 4-year follow-up.

Case 3 A 2-year-old boy presented with a *Proteus* urinary tract infection. An IVU demonstrated bilateral double ureters with bilateral renal, right ureteric and bladder calculi. On micturating cystography there was bilateral Grade IV VUR to the lower poles of both kidneys Surgical treatment was staged, the initial operation being removal of the right renal, ureteric and bladder calculi with reimplantation of the right double ureters, 2 months

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later he had a lower pole left heminephroureterectomy to remove the stones and the non-functioning lower moiety.

The post-operative course was uneventful but follow-up investigations 4 months later revealed a stone in the right upper pole ureter and VUR into a small lower pole left ureteric remnant The stone was removed and the ureteric stump was excised. In the 5 years since operation he has remained symptom-free with satisfactory renal function and no further stone formation.

Case 4. A male infant 6 months of age presented with haematuria. Until that time he had been a healthy breast-fed child. An MSU subsequently grew *Proteus* organisms >100,000 organisms/ml. An IVU showed clubbed calices, dilated ureters and left renal calculi. A micturating cystogram showed right VUR, a filling defect in the bladder and left ureter but no VUR on that side. At operation 5 left renal, 6 left ureteric and 2 bladder calculi were removed and the left ureter was reimplanted. Biochemical analysis of the calculi showed typical mixed stones of an infective type.

A repeat micturating cystogram 6 months later showed a dilated left ureter with some VUR. There was no right VUR and an IVU showed less dilatation on that side. One year later the left ureter was reimplanted for persistence of left VUR. When reviewed 6 years later an IVU showed good renal growth, normal excretion and no recurrence of the calculi.

Case 5. A 2-year-old boy presented with an *Escherichia coli* urinary infection after a 6-month history of intermittent screaming attacks. Investigations revealed a bladder stone and Grade III right VUR. A biochemically mixed bladder stone was removed and the patient began a course of long-term prophylactic antibiotics. A follow-up IVU and a micturating cystogram 5 years later showed resolution of the VUR and no further stone formation.

The clinical findings in these 5 infants and children are summarised in the Table. The calculus disease with VUR resulted in the loss of 2 kidneys (Cases 1 and 2) and the lower half of a kidney (Case 3). The infecting organism was *Proteus* in 4 of the 5 patients. The VUR was probably primary in 4 patients and secondary in 1 (Case 5).

Discussion

These 5 patients are the sum experience of VUR and urinary calculi in the practice of one of the authors (J.D.A.). This includes treating over 1000 patients with VUR and approximately 60 with calculi. Thus the incidence of calculi in patients with VUR is 0.5% and the incidence of VUR in patients with calculi is 8.0%. A preponderance of males (4:1) was found in this small series and a common factor was the presence of a urinary sepsis. In 4 of 5 patients this was due to *Proteus*. The lithogenic role of the *Proteus* organism has been well described in infants and children and it is isolated in 50 to 65% of patients with urolithiasis associated with infection (Malek and Kelalis, 1975; Bensman *et al.*, 1983).

Despite the frequency of urinary tract infection, only 1% of cases are associated with calculi (Malek, 1985). It is possible that infection and anatomical or functional abnormality promote rather than initiate calculus formation, especially as metabolic abnormalities may be found in 30% of stones associated with urosepsis (Churchill *et al.*, 1980). No metabolic abnormalities were detected in our patients.

Isolated bladder stones are rarely seen in developed countries (Marks, 1974), although they may be present in 16% of patients with urolithiasis (Bensman *et al.*, 1983). In countries such as India,

Table Clinical Features of Patients with Urinary Calculi and Vesicoureteric Reflux

					Site of stone							
					Kidney		*Ureter*		*Bladder*	*VUR*		
Case no.	*Age*	*Sex*	*Clinical presentation*	*Urinary pathogen*	*RT*	*LT*	*RT*	*LT*		*RT*	*LT*	*Comment*
1	4 10/12	M	Renal failure Failure to thrive	*Proteus*	✓	—	✓	—	—	✓	✓	Perinephric abscess ? Primary VUR
2	4 2/12	F	Pyelonephritis	*Proteus*	—	✓	—	—	—	—	✓	Perinephric abscess ? Primary VUR
3	2 10/12	M	Pyelonephritis	*Proteus*	✓	—	✓	—	✓	✓	✓	Double ureters Primary VUR
4	6/12	M	Haematuria	*Proteus*	—	✓	—	✓	✓	✓	✓	Primary Lt VUR Secondary Rt VUR
5	2 6/12	M	Urinary infection	*E coli*	—	—	—	—	✓	✓	—	Secondary Rt VUR

where they are endemic, 50% are associated with VUR. In these countries most calculi are in males and related to dietary deficiency in lower socio-economic groups (Aurora *et al.*, 1970). In developed countries they are often associated with bladder outlet abnormalities or foreign bodies (Marks, 1974; Taneja, 1975). The secondary VUR probably results from a combination of inflammatory oedema of the bladder, detrusor spasm and intermittent bladder obstruction (Taneja, 1975). In the absence of a predisposing factor, simple removal of the calculus and control of the urinary infection results in cure of the VUR in over 90% of patients, although severely refluxing ureters (Grades III and IV) often require reimplantation (Taneja, 1975). Recurrence of bladder stones after removal is extremely rare (Aurora *et al.*, 1970).

Urolithiasis is associated with duplication in about 7% of cases in adults (Payne, 1959) but only in 1% in children (Malek, 1985). It is postulated that the presence of obstruction (more common in the upper pole ureter) or VUR (more common in the lower pole ureter) produces stasis, predisposing to infection and stone formation (Amar, 1972). Renal stones in duplication occur more frequently in the lower moiety than the upper (Payne, 1959). Surgical management aims at removing the calculi and correcting any underlying predisposing abnormality. This may include reimplantation of the refluxing ureter or, in the presence of poor renal function, of a moiety heminephroureterectomy. Blind-ending refluxing ureters should be completely excised as calculi can reform (Amar, 1972).

The concurrence of primary VUR and urinary calculi in infants and children has been infrequently reported. A single case in a 3-year-old girl with a staghorn calculus and primary VUR has been described (Lue *et al.*, 1982) in a series of 50 patients of all ages with staghorn calculi and VUR. In another series of 16 patients with VUR and calculi there was 1 child (Amar *et al.*, 1968) and VUR has been found in 9 of 78 (Malek and Kelalis, 1975) and 5 of 38 (Churchill *et al.*, 1980) cases of stones in children. In these series, however, there was no mention of the mechanism of the VUR. The rarity of the association has led to the postulation that VUR actually protects against stone formation (Kuntz, 1977).

The presence of stones is probably an indication for the reimplantation of a primary refluxing ureter, although little is known of the natural history of the VUR if the stone is simply removed.

The prognosis in our series has been good despite the need to remove 2½ kidneys. All except 1 patient (Case 1) have normal renal function with no recurrence of calculi after a 4- to 10-year follow-up. In the absence of abnormal renal function on presentation (Case 1) the outlook should be more guarded.

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Diagnosis and Treatment of Patients with Renal Trauma

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Summary—In this selective study, 59% of the patients had a renal injury (laceration, rupture or pedicle injury). A normal IVU excluded significant renal injury after blunt trauma. Renal angiography was more accurate than ultrasonography or computed tomography in determining the extent of the injury. A retroperitoneal haematoma found during laparotomy should be explored if significant renal trauma cannot be excluded. Renal salvage after rupture or pedicle injury should be attempted in stable patients.

The successful management of renal trauma depends on the accurate assessment of its extent. Its severity is revealed by surgical exploration in patients who require immediate operation due to associated intra-abdominal injuries. However, in some penetrating, (and most blunt) injuries, the extent is assessed by radiological means and the decision as to the best method of treatment is based on these findings.

Ideally, radiological investigations should be able to differentiate between minor and major renal parenchymatous lesions and to identify significant renal pedicle injuries.

Most authors agree that renal contusions and minor lacerations are best treated non-surgically and that major ruptures and pedicle injuries should undergo surgical exploration (Sagalowsky *et al.*, 1983). Some controversy exists over the treatment of major lacerations (Cass *et al.*, 1987; Yarbro and Fowler, 1987). The records of patients treated for renal trauma were assessed with special reference to the accuracy of radiological methods in the assessment of the extent of trauma.

Patients and Methods

We reviewed the case notes of 83 patients treated for renal injury in this hospital between 1976 and 1985. This hospital serves as a referral hospital for acute and elective urological, gastroenterological and cardiovascular surgical problems in adults.

Of the 83 patients, 31 arrived directly at the hospital, 34 were transferred after first aid from other non-trauma hospitals and 18 were sent from the regional trauma centre after the renal trauma was diagnosed.

The mean age of the patients was 33 years (range 13–80) and 60 were males. For the purpose of analysis the patients were divided into 3 diagnostic groups: (1) penetrating injuries (P), (2) blunt injuries, where surgical treatment was undertaken because of intra-abdominal haemorrhage without pre-operative diagnosis of renal injury (B/A), and (3) blunt injuries where the method of treatment was based on the assessment of the extent of the renal injury (B/B).

Classification of the renal injury was based on the system of Sargent and Marquardt (1950) and included grade 1: contusion; grade 2: laceration; grade 3: rupture/perforation; grade 4: pedicle injury. The grade was determined by the combination of all available radiological and clinical information in the non-surgically treated cases.

Shock on arrival was defined as systolic blood pressure <90 mm Hg. Fever as a complication after non-surgical treatment was defined as a temperature of more than 38.5°C for more than 2 days. Significant haematuria included continuing gross haematuria requiring blood transfusion.

The following abbreviations for the radiological investigations were used: IVU: intravenous urog-

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raphy, RA: renal angiography; US: ultrasonography; CT: computed tomography.

Results

The number of patients, the severity of the renal injury and the presence of shock, gross haematuria and associated injuries in the 3 diagnostic groups are shown in Table 1. There were 33 associated injuries after penetrating trauma, the most common being liver (6), diaphragm (5) and colon (4). After blunt trauma the most common of the 95 associated injuries were extremity (21), chest/diaphragm (20), head/neck (16) and liver, spleen and mesentery (6 each).

Diagnosis

Penetrating injuries (P). In 13 patients surgical exploration was undertaken after initial evaluation and resuscitation; 1 patient with a stab wound of the back was treated non-surgically after assessment with IVU (perirenal haematoma) and RA (extravasation).

Blunt injuries (B/A). Sixteen patients were operated on because of intra-abdominal haemorrhage. In addition to other injuries, a retroperitoneal haematoma was found in 14 patients. Gerota's fascia was explored in 10/14 cases and the renal injury was classified as contusion in 2, laceration in 1, rupture in 5 and pedicle injury in 2. Four patients with a retroperitoneal haematoma did not undergo exploration of Gerota's fascia. Post-operative renal angiography revealed a pedicle injury in 2 cases (thrombosis of renal artery, traumatic renal arteriovenous fistula) and renal contusion in 1. The fourth patient was found to have a renal rupture at autopsy. In 2/16 patients, both with gross haematuria, no retroperitoneal haematoma was encountered. A severe renal injury (grade 2–4) was excluded by exploration of Gerota's fascia in 1 case and by palpation (and post-operative radiological investigations) in the other.

Table 1 Clinical Data on 83 Patients with Renal Trauma

	Diagnostic group		
	P	*B/A*	*B/B*
No. of patients	14	16	53
Grade 1	—	5	29
Grade 2	4	1	15
Grade 3	5	6	9
Grade 4	5	4	—
Shock on arrival	9	7	2
Gross haematuria	5	8	31
Isolated renal trauma	—	—	28
Average no of associated injuries/patient	2.4	3.7	0.7

Blunt injuries (B/B). All of the 53 patients had either gross (31) or microscopic (22) haematuria. The degree of haematuria did not reflect the severity of the injury. IVU was performed in 43 cases (Table 2). RA, US and/or CT were performed in 27 patients; 21 of them also had IVU (Table 3). The degree of the renal trauma was confirmed operatively in 7/53 cases.

Table 2 Results of IVU in 43 Patients with Blunt Renal Trauma

	Grade			
Finding	*1*	*2*	*3*	*Total*
Normal	15	—	—	15
Delayed function/ incomplete filling	4	6	3	13
Extravasation	—	8	4	12
Non-function	—	1*	2	3
Total	19	15	9	43
Not done	10	—	—	10

*Pre-existing hydronephrosis

Treatment

Primary surgical treatment was given to 13/14 patients with penetrating injury and—by definition—to all 16 patients in group B/A. Of the 53 patients with blunt injury who were subjected to diagnostic investigations (group B/B), 6 (11%) underwent surgical exploration. The indications for exploration were: rupture of a hydronephrotic kidney, non-function on IVU, total rupture in renal angiography, extravasation on IVU in a horseshoe kidney and incomplete filling on IVU together with the clinical picture (2 cases). Non-surgical treatment was given to 47/53 patients, 1 of whom required delayed surgery for renal trauma. The methods of treatment are summarised in Table 4.

Table 3 Results of Renal Angiography (RA), Ultrasonography (US) and Computed Tomography (CT) in 27 Patients with Blunt Renal Trauma

	Grade		
	1	*2*	*3*
RA			
Laceration	—	8*	—
Fragmentation	—	—	6**
Non-function	—	1†	—
US			
Normal	7	—	—
Intrarenal/subcapsular haematoma	3	1	—
Perirenal haematoma	—	1	2
CT			
Normal	1	—	—
Perirenal haematoma only	—	—	1
with parenchymal defect	—	2**	2

*With extravasation in 2 cases and with perirenal haematoma in 2 cases

**With extravasation in 1 case.

†Pre-existing hydronephrosis

Table 4 Method of Treatment of 83 Renal Injuries

	Grade				
Treatment	*1*	*2*	*3*	*4*	*Total*
Nephrectomy	—	1*	6	2	9
Partial nephrectomy	—	—	4**	—	4
Suture	—	1	3	—	4
Exploration/drainage	4	2	—	—	6
Vascular repair	—	—	—	5	5
Laparotomy only	1	2	2†	2††	7
Non-surgical	29	14	5‡	—	48

*Pre-existing hydronephrosis

**One required delayed nephrectomy

†Both died peri-operatively

††In both cases a retroperitoneal haematoma was not explored during laparotomy for associated injuries.

‡One required delayed suture of renal rupture.

Mortality

There were 5 deaths: 2 after penetrating and 3 after blunt injuries (all in group B/A). None was attributable to the renal injury. Four patients died as a result of haemorrhage from associated intra-abdominal injuries within 48 h of the trauma: 1 patient died from hepatic failure 10 days after a severe liver injury.

Morbidity

In 47 patients there were no complications: 6/14 after penetrating injury, 3/16 (B/A) and 38/53 (B/B) after blunt trauma. The remaining 31 survivors had a total of 57 complications. The most common non-renal complications were hepato-biliary (9), pulmonary (5) and wound complications (4). Renal complications after non-surgical treatment included significant haematuria (4 patients), fever (4), urinary tract infection (2) and temporary hydronephrosis (1).

Reversible renal insufficiency after nephrectomy was detected in 2 of the surviving patients. Post-operative urinary leakage complicated partial nephrectomy on 2 occasions and renal suture on 1.

In 2 cases a pedicle injury was missed at initial laparotomy. One of these patients developed a non-functioning kidney due to thrombosis of the renal artery. In the other case a renal arteriovenous fistula formed, requiring reoperation. The kidney was saved with normal function and no hypertension developed. A vascular repair (suture of renal artery in 3, suture of renal vein in 1 and suture of artery and ligature of vein in 1) was performed in 5 patients with a pedicle injury. In 3 of the 4 survivors a functioning kidney resulted, but 1 subsequently developed hypertension. In the fourth case a non-functioning kidney resulted. The patient has been followed up for 3 years without signs of hypertension.

The mortality and morbidity statistics of the 3 diagnostic groups are summarised in Table 5.

Discussion

The high proportion of severe renal injury (grade 2–4: 49/83) in our patients, when compared with the proportion reported in other series (Fowler *et al.*, 1982; Bergren *et al.*, 1987), reflects the position of this hospital as a referral hospital with a special urological unit. Thus in many cases either the suspicion or the diagnosis of the renal injury existed on arrival and the main purpose was to determine the severity of the injury and the appropriate treatment. In this selective sample, both contusions and severe multi-trauma cases are under-represented, as they were treated elsewhere.

Diagnosis

A normal IVU in patients with blunt injuries excludes severe renal injury (Bergren *et al.*, 1987). Non-visualisation or extravasation is a significant finding for severe renal injury, but delayed function

Table 5 Mortality and Morbidity in 83 Patients with Renal Trauma

	Diagnostic Group			
	P	*B/A*	*B/B*	*Total*
No. of patients	14	16	53	83
Average severity of renal trauma	3.1	2.6	1.6	2.0
No. of deaths	2	3	—	5(6%)
No. of survivors with complications	6	10	15	31(37%)
Hospital stay among survivors				
Mean (days)	18	38	9	15
Range (days)	8–45	10–90	1–27	1–90
Renal salvage*	8/12	9/14	51/52	68/78(87%)

*Excluding 4 peri-operative deaths and 1 pre-existing hydronephrosis

of incomplete filling on IVU is non-specific and requires further investigation (Fowler *et al.*, 1982; Sagalowsky *et al.*, 1983; Cass, 1983; Bergren *et al.*, 1987). Without exception, these features could be seen in our patients.

Ultrasonography has been recommended as a good adjunctive study in evaluating renal trauma and excluding post-traumatic renal problems (Kay *et al.*, 1980). In the present series, US showed perirenal and intrarenal haematomas but, taken in isolation, could not accurately determine the severity of the renal injury. However, normal US seems to exclude severe parenchymal lesions.

Computed tomography is an anatomical study which allows for a precise morphologic determination of the injury. Good results have been reported with contrast CT both with blunt and penetrating injuries (McAninh and Federle, 1982; Carroll and McAninh, 1985). When renal vascular injury is suspected, renal angiography is still recommended, although CT may be valuable when time does not allow an angiogram to be performed (Cass, 1983; Sclafani, 1986). In our experience, CT differentiated contusion from renal parenchymal defects and showed the presence of a perirenal haematoma, but was unable to assess the extent of the parenchymal lesion (laceration versus rupture).

Selective renal angiography can assess the extent of the parenchymal injury and show the vascular anatomy and pedicle damage and should be carried out when an exact diagnosis cannot be made on an IVU (Fowler *et al.*, 1982). Our results showed that RA was the only method which could differentiate between renal laceration and rupture. It also showed the circulatory status of a loose, displaced fragment. Although none of the patients with renal pedicle injury underwent pre-operative radiological investigations, it can be assumed that RA is helpful if the condition of the patient permits pre-operative investigations.

Treatment

Surgical exploration should be performed in patients with penetrating trauma and haematuria or where injury to the main renal artery or devascularisation of the majority of the renal parenchyma is found on renal angiography after blunt trauma (Sagalowsky *et al.*, 1983). This study also confirms that the remaining patients can be treated non-surgically with satisfactory results.

Most of our patients with renal rupture or pedicle injury underwent surgical exploration, mostly due to intra-abdominal haemorrhage after blunt trauma or due to a penetrating injury. It has been recommended that if an expanding retroperitoneal haematoma is found during laparotomy, or if a significant renal injury is suspected, exploration of Gerota's fascia should be performed (Sagalowsky *et al.*, 1983; Cass *et al.*, 1985; McGonigal *et al.*, 1987). Four of our 14 patients with retroperitoneal haematoma found during laparotomy after blunt trauma did not undergo exploration of Gerota's fascia, which resulted in 2 missed pedicle injuries and 1 missed rupture. Although renal exploration increases the rate of nephrectomy, and not all retroperitoneal haematomas result from renal injury (Sagalowsky *et al.* 1983; McGonigal *et al.*, 1987), exploration of Gerota's fascia in patients with retroperitoneal haematoma seems to be indicated when pre- or per-operative radiological investigations do not exclude severe renal trauma. However, the importance of obtaining proximal and distal control of the great vessels before exploration must be emphasised.

The total nephrectomy rate (immediate+delayed) in renal ruptures was 7/20 in this study. Partial nephrectomy or suture results in renal salvage in the majority of cases and should be tried under favourable conditions.

Turner *et al.* (1983) reported 10% renal salvage after arterial and 51% after renal vein injuries. The presence of renal arterial flow at the time of repair was of prime importance in renal salvage. In our study, 9 patients had renal pedicle injuries. All underwent immediate operation, although on 2 occasions Gerota's fascia was not explored. Vascular repair was attempted in 4 surviving patients and a functioning kidney without hypertension resulted in 2 cases. Because renal vascular injury usually coexists with severe associated injuries, it seems that vascular repair should be attempted only in stable patients under favourable conditions and when flow in an injured artery is preserved.

In conclusion, normal IVU after blunt trauma excludes severe renal injury. If the IVU is pathological, renal angiography is better than ultrasonography or computed tomography in determining the extent of the injury. If a retroperitoneal haematoma is found during laparotomy, it should be explored if a severe renal injury cannot be excluded. Renal salvage after rupture or pedicle injuries should be attempted in stable patients.

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Urothelial Tumours of the Upper Urinary Tract

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Summary—We present a retrospective 10 year analysis of 76 patients with urothelial tumours of the upper urinary tract. Patients older than 65 years, and female patients, presented with more advanced stages and had a worse prognosis. The grade and stage of the tumour has the greatest impact on survival. No conclusions can be drawn on the efficacy of various types of surgery, but simple nephrectomy gave a 5-year survival of 68%, with a stump recurrence rate of 15%.

We observed that patients with urothelial tumours had 4 fold increased chance of developing gastrointestinal cancer.

Urothelial tumours of the upper urinary tract are rare. In most countries, tumours of the renal pelvis and ureter are usually classified as kidney and bladder neoplasms and limited data are available on their epidemiology. In Sweden, the incidence rates are 1.5 and 0.9/100,000 for males and females respectively (National Board of Health and Welfare, 1980). These low incidence rates prevent the accumulation of patients for randomisation of treatment and management remains controversial (Kim *et al.*, 1972; Petkovic, 1972; Brown and Roumani, 1974; Strong and Pearse, 1976; Strong *et al.*, 1976; Heney *et al.*, 1981; Pagano, 1984).

Simple nephrectomy for renal pelvic tumours results in a 12% 5-year survival rate (Humphreys and Fost, 1960) and creates an incidence of recurrence in the ureteric stump of 4 to 64% (Grabstald *et al.*, 1971; Johansson *et al.*, 1976; Strong *et al.*, 1976; Kakizoe *et al.*, 1980). For this reason many authors prefer nephroureterectomy, with excision of a bladder cuff, as the standard form of treatment for upper urinary tract urothelial tumours (Strong and Pearse, 1976; Clayman *et al.*, 1983; Auld *et al.*, 1984). On the other hand, Vest (1945) suggested a more conservative surgical approach in selected patients with benign tumours. More conservative treatment has subsequently received considerable support (Firstater, 1960; Gibson, 1967; Petkovic, 1972; Brown and Roumani, 1974; Johnson and Barbarian, 1979; Pagano, 1984; Bazeed *et al.*, 1986).

The controversy in the treatment of upper urinary tract urothelial tumours has prompted us to review our experience over the last 10 years and the aim of this study was to determine the various prognostic factors that could affect survival.

Patients and Methods

A review was made of the case records and relevant information on 76 patients with tumours of the ureter and renal pelvis who were treated between January 1975 and December 1984; 49 patients were male and 27 female (1.8:1), with an age range of 42 to 84 years (mean 67).

All patients had histologically proven urothelial tumour of the upper urinary tract; 74 patients had transitional cell carcinoma (TCC) and 2 had squamous cell carcinoma; 34 patients had right-sided and 41 had left-sided tumours (1:1.12). There was 1 synchronous bilateral tumour.

Gross painless haematuria was the most common complaint at presentation in 74% of patients. Pain was the initial symptom in 13%, weight loss and malaise in 5%. Intravenous urography (IVU) revealed a filling defect in the collecting system in 38% of patients and a non-functioning kidney in another 27%. While signs of obstruction were the only abnormality in 14%, 21% of the IVUs revealed more than 1 abnormality; 13 patients (17%) had a

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history of bladder tumour diagnosed and treated in the past.

IVU, blood count, kidney and liver function tests, chest X-ray and cystoscopy were performed in all patients. Ascending pyelography, liver, bone and brain scans, CT scans and other investigations were performed where necessary.

Renal pelvic or caliceal tumours were found in 52% of the patients; 29% had ureteric tumours and 19% had multiple tumours in the upper tract, 15 of 21 ureteric tumours were located in the lower third of the ureter.

Clinical and pathological staging was made by using the UICC (1978) classification. Lymph node status was not studied clinically and only nodes obtained during biopsy of patients with metastatic disease were found positive. Nine patients had metastatic disease at presentation; 3 patients had liver metastases (1 also in the contralateral adrenal gland); 3 bone, 2 lung and 1 bowel secondaries were noted. Histological grading was made according to the World Health Organisation criteria for cytohistological differentiation of transitional cell carcinoma (Mostofi *et al.*, 1973).

One patient whose tumour was completely resected died from heart failure in the peri-operative period and 2 patients were lost to follow-up. The remainder were followed up regularly (minimum 8 months and maximum 11 years; mean 68 months). Regular cystoscopies were performed over a 5-year period and subsequently only when indicated. Three patients were followed up by urine cytology only; 1 patient whose tumour was excised locally was followed up by ureterorenoscopy on 2 occasions. All other patients were reviewed as mentioned above.

Patients who were lost to follow-up, but who died of other causes, were included in the analysis of data by the Berkson and Gage life-table method (Armitage, 1971). Absolute survivors were compared statistically using Fisher's chi-squared test.

Results

Patients with high grade tumours presented in more advanced stages. The slides of 2 patients, 1 with pT3 and 1 with pT4 tumour, reported as grade I were re-reviewed. It is interesting to note that even the slides of deep sections showed grade I TCC.

A total of 41 patients underwent simple nephrectomy (54%); 17% had a nephroureterectomy and 15% had a nephroureterectomy with excision of bladder cuff; 7% had local excision of their tumours and 7% were only biopsied due to locally advanced or metastatic disease. After a mean follow-up of 5.6 years 43 patients were alive (58%), 23 patients died because of tumour (31%) and 8 patients (11%) of unrelated causes; 2 patients were lost to follow-up. The overall survival rates are shown in Figure 1.

Figure 2 shows the relationship between survival and the stage of the initial tumour irrespective of the type of treatment. There was no significant difference between the survival rates of patients with pTa or pT1 tumours. Since the number of patients with pT2 and pT3 tumours was small, pTa and pT1 were compared with tumours in more advanced stages (*i.e.* pT2, pT3 and pT4) and this was statistically significant ($P<0.001$).

When survival was compared according to the grade of the tumour, there was a statistically significant difference between the survival rates of patients with GI versus GII and GIII tumours ($P<0.001$). There was no difference between the survival of patients with GII and GIII tumours, but numbers were smaller in these groups (Fig. 3).

Although there were different surgical approaches to these tumours, the extent of disease and patients' survival rates were not statistically significant. The stage and grade of tumours in each treatment group were also similar. Figure 4 shows the actuarial survival rates according to the type of surgery performed. A formal nephroureterectomy gave the most encouraging results. All patients who received biopsies had pT4 tumours and 3 also had metastatic disease. They all died within 2 years.

Nine patients had metastatic disease. All had pT4 disease with involved regional lymph nodes; 6 simple nephrectomies and 3 biopsies were performed. All patients died within 7 months (mean interval 3 months).

In 61 patients no further treatment was required apart from the initial surgery; 7 patients required surgery for recurrent tumour on the same side; 5 patients received systemic chemotherapy, 1 local chemotherapy and 2 received radiotherapy.

Of the 41 patients who were given a simple nephrectomy, 6 had a recurrence in the stump producing a recurrence rate of 15%. The mean interval until recurrence in the ureteric stump was 37 months (maximum 125 months). One of the 13 patients who underwent nephroureterectomy had a recurrence in the ureteric orifice that was left *in situ*. There was no difference between the survival rates of patients with or without recurrences. No criteria were found to predict stump recurrence. None of the local resections showed recurrence anywhere in the urinary tract after a mean follow-

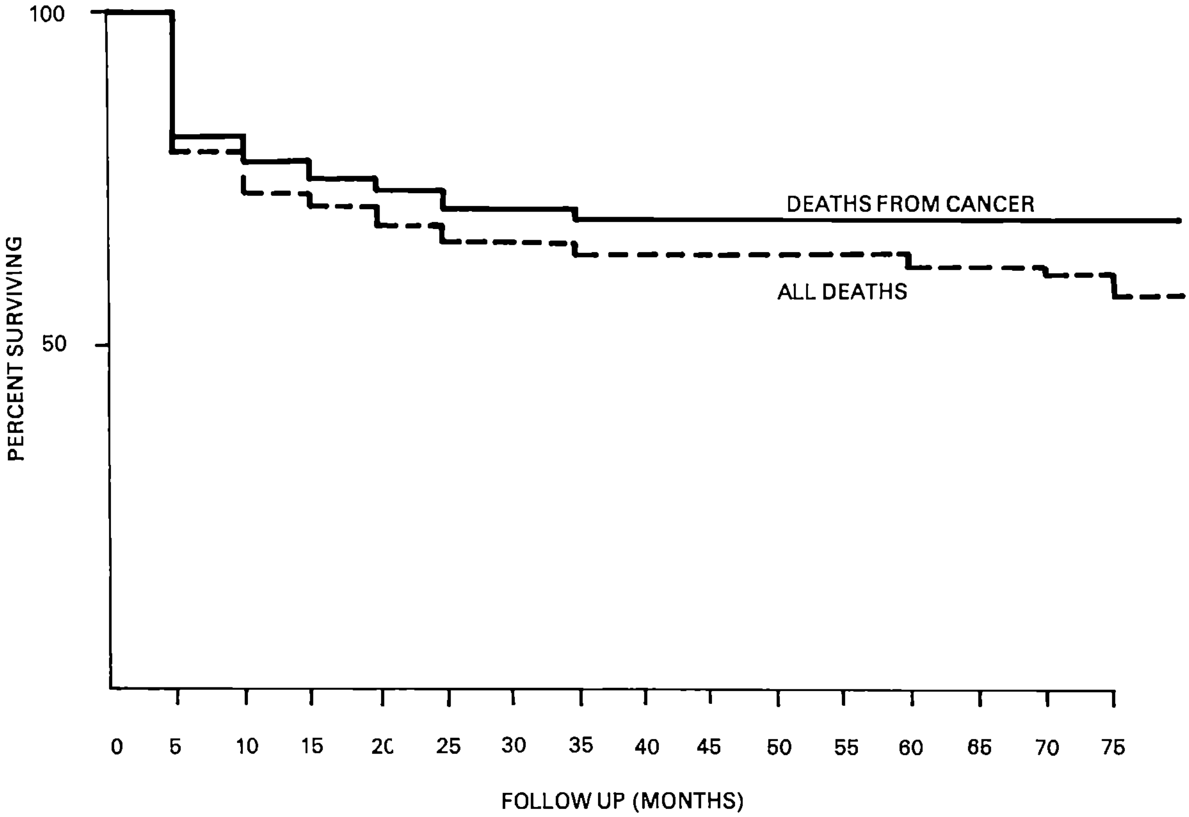

Fig. 1 Actuarial survival rates for ureteric and renal pelvic tumours (all stages).

up of 48 months. There was no recurrence in the contralateral system.

In 36% of patients a bladder tumour was found at diagnosis or during the follow-up period. Thus 44% of all patients developed a bladder tumour prior to, at or after diagnosis. Patients with bladder tumours were all dealt with by endoscopic means and in some cases, with additional intravesical chemotherapy. No patient required cystectomy or died of bladder tumour.

Eleven patients with a non-functioning kidney on IVU at presentation died of their tumour, whereas only 3 patients with filling defects died ($P<0.05$); thus a non-functioning kidney on IVU indicates a poor prognosis.

Patients over the age of 65 had a worse prognosis than younger patients ($P<0.05$). Similarly, female patients had a worse prognosis than males ($P<0.05$). However, both of these groups had more extensive tumours (pT2, pT3 and pT4) at presentation than the others ($P<0.05$).

Although patients with ureteric tumours and multiple tumours in the upper tract were in more advanced stages (pT2, pT3 and pT4) than those with renal pelvic or caliceal tumours ($P<0.05$), there was no statistical significance among their survival rates. Eight patients (11%) developed a second malignancy during the follow-up period and 6 (8%) had adenocarcinoma of the gastrointestinal system.

Discussion

The search for the optimum treatment for urothelial tumours of the upper urinary tract is incomplete, due mainly to the lack of properly controlled, prospective randomised trials. This study, which is also retrospective, does not aim to compare the efficacy of one treatment with another, but tries to present some facts which may help the surgeon to choose his own approach.

Our overall survival rates are similar to those

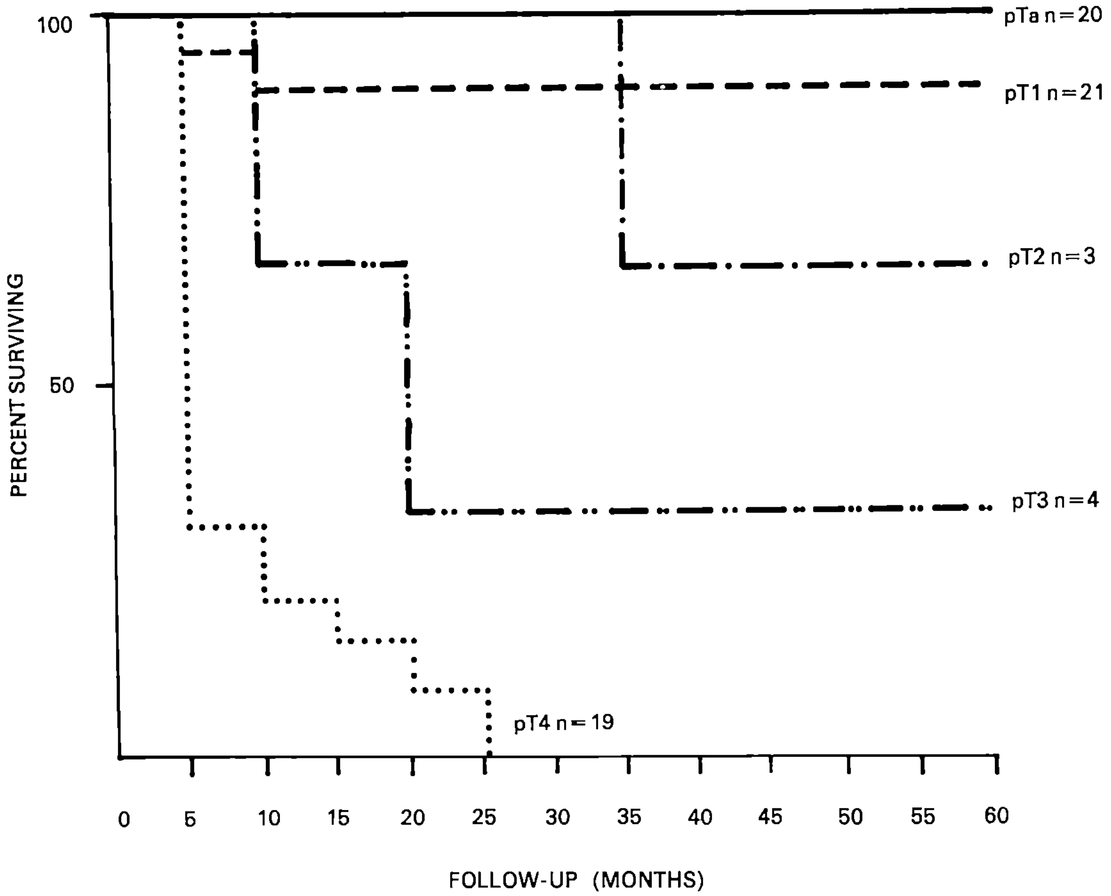

Fig. 2 Actuarial survival rates of patients with uroepithelial tumours of the upper urinary tract according to the initial stage of the tumour (deaths from other causes are excluded)

reported previously (Kim *et al.*, 1972; Batata *et al.*, 1975; Heney *et al.*, 1981; Wallace *et al.*, 1981). Deaths from cancer usually take place within 1 year and few deaths should be expected after 2 years. The initial grade of the tumour is a prognostic indicator of survival. In our study, the 5-year survival rates for GI, II and III tumours were 94, 58 and 17% respectively. These are better than the rates reported by Batata *et al.* (1975) (78, 50, 0%) but worse than those of Heney *et al.* (1981) (100, 81, 29%). The initial stage of the tumour is also of prime significance in survival. Once the tumour invades the muscle there is a sharp decline in survival rates. Our 5-year survival rates correlate well with others (Batata *et al.*, 1975; Heney *et al.*, 1981). In all these series, patients with pT4 tumours died within 3 years.

It is agreed that the type of operation does not seem to play a direct role, or is of secondary importance in the final outcome (Batata *et al.*, 1975; Strong and Pearse, 1976; Heney *et al.*, 1981; Wallace *et al.*, 1981). In this series, nephroureterectomy with excision of a bladder cuff produced the best results, but the number of patients who had local excision of their tumours was too small to draw any conclusions. We found no difference between the survival of patients who had nephrectomy and nephroureterectomy. Therefore there seems little point in removing the whole ureter unless the intramural segment, with an area of surrounding bladder wall, is also removed. Nephrectomy, with removal of as much ureter as possible from the incision, is a simple and safe operation for elderly patients with urothelial tumours and gives a 5-year survival rate of 68%; *i.e.* higher than that reported previously (Humphreys and Fost, 1960; Petkovic, 1972). Our stump recurrence rate (15%) is lower than the figures reported by many others

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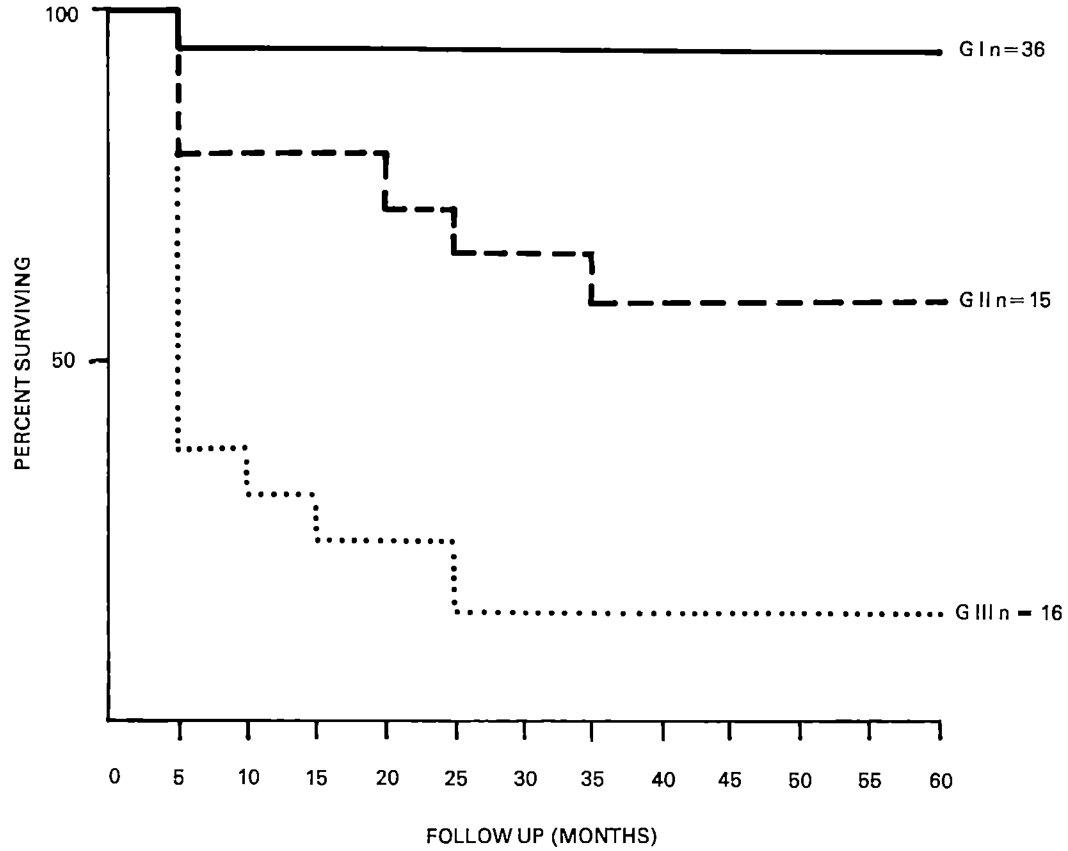

Fig. 3 Actuarial survival rates of patients with uroepithelial tumours of the upper urinary tract according to the initial grade of the tumour (deaths from other causes are excluded)

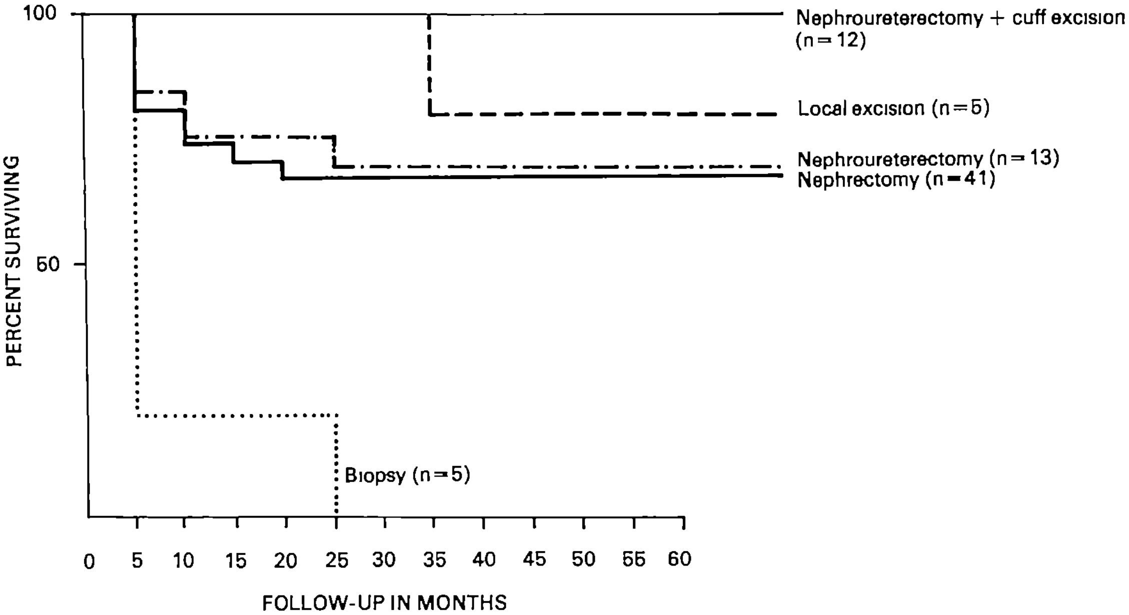

Fig. 4 Actuarial survival rates of patients with epithelial tumours of the upper urinary tract according to the type of surgery performed (deaths from other causes are excluded)

(Strong and Pearse, 1976), again suggesting the benign nature of these tumours in this region. While more extensive surgery does give higher survival rates, it also raises the question of whether more kidneys could have been saved with a local excision. Endourological techniques with percutaneous nephroscopy, biopsy and fulguration (Streem and Pontes, 1986), transurethral ureterorenoscopic diagnosis and treatment (Huffman *et al.*, 1985) and destruction of the tumour with laser (Bagley, 1986) are attractive and promising methods of parenchyma-sparing treatments. We believe that the main problem in the early detection of recurrence in the upper tract or in the stump can be overcome with more accurate and advanced diagnostic techniques, particularly ureterorenoscopy (Pagano, 1984; Huffman *et al.*, 1985). Bladder tumours have been followed up regularly by endoscopy since the beginning of this century and tumours of the upper tract could be followed in the same manner.

Our figures for concurrent or subsequent bladder tumour are similar to those reported by others (Batata *et al.*, 1975; Strong and Pearse, 1976; Kakizoe *et al.*, 1980; Wallace *et al.*, 1981; Auld *et al.*, 1984). However, while all of the bladder tumours in our series were controlled by endoscopic surgery, 75% of patients reported by Kakizoe *et al.* (1980) required radical cystectomy.

Histopathological changes adjacent to and remote from the tumour, indicating multifocality of disease, is the reason for more extensive surgery given by some authors (Kakizoe *et al.*, 1980; Auld *et al.*, 1984). We believe that this should be an indication for a more conservative approach, for whilst these mucosal changes probably do exist, they may not progress. Secondly, it is rather aggressive to remove the entire urothelium, in the light of improvements in supervision of the urothelium by cytology, cystoscopy and ureterorenoscopy with biopsy.

Pathological stage and grade of the tumour have the greatest impact on survival. Urine cytology and clinical staging, incorporating ureterorenoscopy and combined with operative findings, may be the deciding factor in the final choice of operation.

Another interesting finding in this series is the high incidence of a second malignancy. Batata *et al.* (1975) also mentioned that 3 (2 with adenocarcinoma of the gastrointestinal system) of their 41 patients with ureteric tumours had had extra-urothelial malignant tumours treated in the past. The calculated age-specific rates for 65 to 74-year-old males in 1980 was 403.45/100,000 population for adenocarcinoma of the gastrointestinal system (*i.e.* higher than females) (Scottish Health Services, 1984).

It was concluded that patients with urothelial tumours of the upper urinary tract have a 4-fold increased chance of developing a second gastrointestinal malignancy. Teppo *et al.* (1985) found no such coexistence in an epidemiological study of multiple cancer in Finland. We believe that our findings are interesting because the relative risk posed by a new primary cancer should decrease with increasing age at diagnosis of the first cancer (Teppo *et al.*, 1985).

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Testing the Chemosensitivity of Renal Carcinoma *in vitro*

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Summary—Tumour cells from 23 renal carcinomas were exposed *in vitro* to increasing concentrations of medroxyprogesterone acetate (MPA) or one of several cytotoxic agents. Thereafter the uptake of ^{75}Selenomethionine (^{75}SeM) was compared to that of tumour cells not exposed to the drug.

Using drug concentrations similar to those seen following *in vivo* administration in patients, MPA produced $\geq 50\%$ inhibition of ^{75}SeM uptake in 5 of 23 cases. The comparable proportion for doxorubicin was 4 of 5 and for mitozantrone 7 of 12. Methotrexate and Vinblastine were much less effective. In all cases where $\geq 50\%$ inhibition was obtained with doxorubicin and mitozantrone the carcinoma had spread beyond the kidney. Thus drug sensitivity may be associated with a high mitotic rate.

Renal carcinomas, with an incidence of 4/100,000, account for 3% of all malignant neoplasms (Kantor, 1977). Some 25% of these patients have metastatic disease at the time of diagnosis, with a death rate of 74% at 1 year and 96% at 3 years (Patel and Lavengood, 1978). The survival rate of patients with localised disease following radical nephrectomy has been reported as 62% at 5 years (Nurmi, 1984) and 56% at 10 years (Skinner *et al.*, 1971).

Apart from surgery, no form of therapy is of proven value in the management of this neoplasm. A variety of hormonal and chemotherapeutic agents has been administered, alone or in combination, but the remission rates have been low (Harris, 1983). Thus a test to screen individual drugs for their effectiveness against particular tumours would be of value. Fleischmann *et al.* (1983) found that the ability of different chemotherapeutic drugs to inhibit the formation of neoplastic cell colonies when applied to renal carcinomas was so variable as to be unsuitable in the assessment of drug sensitivity. Day *et al.* (1981) found identical responsiveness in 2 renal carcinomas to drugs as measured *in vitro* by inhibition of ^{3}H thymidine uptake and *in vivo* by inhibition of tumour growth in athymic mice. Bazeed *et al.* (1988) found only occasional sensitivity of carcinomas to drugs as measured by inhibition of ^{3}H thymidine and ^{3}H uridine uptake *in vitro*. Ferro *et al.* (1988) reported the use of a ^{75}Selenomethionine uptake assay (Liebold and Bridge, 1979) to investigate the *in vitro* cytotoxic effect of stilboestrol on prostate carcinoma cells. We describe the use of this assay to measure the inhibitory action of several hormonal and chemotherapeutic agents on protein synthesis by renal carcinoma cells.

Patients and Methods

General plan of the experiments

A total of 23 patients was studied. In each case a suspension of tumour cells was prepared from the renal carcinoma. The cells were then exposed to a hormonal or chemotherapeutic agent for 24 h, washed to remove the drug and cultured with ^{75}Se (as Selenomethionine) in methionine-free medium for a further 48 hours. The radioactivity incorporated in the cell pellet was an indicator of protein synthesis and was compared with that of cells not exposed to a drug.

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Preparation of tumour cell suspensions

This was as described by Ferro *et al.* (1988) except that incubation with enzymes, to disaggregate the solid neoplasm, was for 1 h. When the tumour cell band, separated following centrifugation on the Nycodenz column, was examined using a haemocytometer, only carcinoma cells were seen and in most cases their viability exceeded 90%.

Exposure to drugs

In the present experiments 1 from each of the major classes of cytotoxic agents was investigated. The drugs used were:

(i) Medroxyprogesterone acetate (Depo-Provera) – a hormonal agent.
(ii) Doxorubicin hychochloride (Adriamycin) – an antibiotic.
(iii) Vinblastine – a vinca alkaloid.
(iv) Methotrexate – an antimetabolite.

In view of the effectiveness of Adriamycin the less toxic, but structurally related agent mitozantrone (Novantrone), was also studied in later patients. Carcinoma cells in aliquots of 10^5 were either exposed for 24 h to a single concentration of a particular agent, or to increasing concentrations.

Incorporation of ^{75}Selenomethionine (^{75}SeM)

This was as described by Ferro *et al.* (1988). From each 1 ml aliquot of carcinoma cells, incorporating ^{75}SeM following exposure to a given concentration of a particular drug, three 0.2 ml samples were obtained and the radioactivity incorporated in the cells was determined. In a separate experiment (Lai, unpublished data), repeat determinations of protein synthesis inhibition following drug exposure were made using a carcinoma cell line HT29. This yielded consistent data. Using mitozantrone, tumour inhibition was directly related to drug concentration.

Statistics

For a given carcinoma all of the values for ^{75}SeM incorporation were subjected to a one-way analysis of variance. The significance of any reduction in counts following exposure to a given concentration of a particular drug was determined in comparison to that for cells not exposed to any drug.

Results

The details of the 23 patients are shown in Table 1. Although 17 patients had tumour spread beyond the kidney, only 4 received drug therapy, 3 with Depo-Provera and 1 with methotrexate. Of the 17 patients, 9 survived for more than 2 years, a further 3 for more than 1 year; 10 of these 17 patients remain well.

The percentage inhibition of protein synthesis and its significance following exposure to drugs are shown for Depo-Provera (Table 2), Adriamycin (Table 3), Novantrone (Table 4), vinblastine (Table 5) and methotrexate (Table 6). The peak plasma concentration and the terminal half-life following standard *in vivo* administration were: Adriamycin 0.24–0.60 μg/ml and 28.1–43.6 h, Vinblastine 0.44–1.37 μg/ml and 17.4–21.8 h, Methotrexate 2.75 μg/ml and 7.6 h (Alberts and Chen, 1980), Novantrone 1.2–1.5 μg/ml and 38.0 h (Hulhoven *et al.*, 1984).

At a concentration of 1 μg/ml Depo-Provera, carcinoma cells from 5 of 23 patients showed $\geq$50% inhibition of protein synthesis. The comparable proportion for Adriamycin was 4 of 5 and for Novantrone 7 of 12 patients. The data for vinblastine and methotrexate are less relevant in that the concentrations of drugs used *in vitro* were greatly in excess of those seen following *in vivo* administration. Despite this, at 10 μg/ml vinblastine, carcinoma cells from only 3 of 12 patients showed $>$50% inhibition of protein synthesis. At 400 μg/ml methotrexate, the comparable proportion was 5 of 12 patients. There was no relationship between responsiveness *in vitro* to a particular drug and the histological pattern of the neoplasm except in the cases of Novantrone (*vide infra*).

Discussion

Using a mouse mammary carcinoma, *in vitro* inhibition of ^{75}SeM uptake was related to the *in vitro* anti-tumour action of the drugs tested (Lai *et al.*, 1989). The unpredictable course of renal carcinoma (Holland, 1973) makes it difficult to evaluate the outcome of any therapy. The relatively long survival of patients with tumour spread beyond the kidney in the present series is a reflection of this. It also questions the necessity of therapy other than nephrectomy. However, if a clear indication of tumour responsiveness could be obtained, administration of the appropriate drug might be indicated in patients with metastases.

In the present study, with the exception of patients 1, 5 and 18, no correlation between *in vitro* and *in vivo* results of treatment was possible as no drug treatment was given. However, in these 3 cases there was good agreement, Harris (1983)

Table 1 Details of Patients

No.	*Age*	*Sex*	*Tumour Size (cm)*	*Degree of spread (stage)*	*Histology*	*Chemotheraphy*	*Results*
1	63	M	6×5×2	IV	Pleomorphic adenocarcinoma Some areas of clear cells Numerous cysts	MPA†	Relief of pain Died 2 years 1 month Progressive disease
2	68	M		IV	Clear cell ca. with some oxyphil cells	MTX‡	
3	74	M	4×5×2	I	Granular and clear ca cells	Nil	A & W* 2 years 9 months
4	60	F	7×8×6	II	Tubular arrangement of ca cells with intervining areas of spindle cells	Nil	A & W 3 years
5	57	M	Diam 10	IV	Solid clear cell ca.	MPA	Relief of pain. Died 8 months Progressive disease
6	67	F	5×4×2.5	I	Clear cell ca	Nil	A & W 3 years
7	70	M	11×10×6	III	Polycystic variant of renal ca	Nil	Died 2 days Myocardial infarct
8	52	F	30×12×15	III	Tubulo-papillary ca.	Nil	A & W 3 years
9	69	M	Cyst diam 11 5	III	Clear cell ca in wall of cyst	Nil	A & W 3 years 4 months
10	68	F	7×7×8	III	Clear cell ca.	Nil	A & W 2 years
11	70	M	8×6×4	III	Clear cell ca	Nil	A & W 1 year 9 months
12	70	M	6×6×6	III		Nil	A & W 1 year 11 months with ca oesophagus
13	70	M	7×7×5	IV	Moderately diff. adenocarcinoma	Nil	Died 4 days Bronchopneumonia. Acute tubular necrosis
14	67	M	Diam 5 5	I	Clear cell ca	Nil	A & W 2 years 2 months
15	51	M	14×12×7	II	Clear cell ca Few mitoses	Nil	A & W 2 years 1 month
16	63	M	Diam 6	IV	Poorly diff ca Mainly clear cells Some epithelial cells	Nil (local DXR)	11 months Unfit to attend clinic
17	77	F	15×11×8	IV	Moderately diff ca Clear cells	Nil	Died 3 days Gastric perforation
18	40	M	19×12×9	IV	Adenocarcinoma Varying cell types and patterns Focal sarcomatous areas	MPA	Died 1 month Progressive disease
19	65	M	12×12×11	IV	Clear cell ca	Nil	Died 5 months Progressive disease
20	51	M	18×9×8	IV	Mixed clear and granular cell ca	DXR	A & W 1 year 10 months
21	54	M	10×9×4	III	Clear cell ca.	Nil	A & W 3 months
22	54	F	Diam 10	II	Clear cell ca. Well differentiated	Nil	Awaiting first follow-up
23	50	M	12×10×9	II	Clear cell ca.	Nil	First follow-up 1 month

All patients underwent a radical nephrectomy

* A & W = Alive and well.

† MPA = Medroxyprogesterone acetate

‡ MTX = Methotrexate.

presented data for the number of objective responses in patients with renal carcinoma treated with progesterone. The figure of 10% in 300 patients, compared with 22% for ≥50% inhibition of protein synthesis recorded in the present study is of great interest. Heim *et al.* (1981) reported an objective response rate of 24% among 135 patients treated with vinblastine. This compares with 25% of renal carcinomas showing inhibition of protein synthesis when exposed *in vitro* to vinblastine (*vide supra*).

Oliver *et al.* (personal communication) treated 12 patients with bulky rapidly progressive renal

Table 2 Percentage Inhibition of ^{75}SeM Uptake by *in vitro* Exposure to Depo-Provera[1]

Patient no.		*Conc µg/ml*			
		0.1	1.0	5.0	10 0
1			66 0§		
2			16 0*		
3			28.0†		
4			54.0§		
5			Nil		
6			Nil		
7			50.0§		
8			5 0		
9			86.0§		
10			Nil		
	culture 8 days		Nil		
11			77 0§		
12			Nil		
13			20 0*	Nil	14 0
14			15.0*	8 0	26 0‡
15			6 0	Nil	Nil
16			Nil	Nil	Nil
17			22 0‡	24.0‡	81.0§
18			2 3	Nil	69 0§
19			20 8§	42 8§	
20		0 8	7 4		7 7
21			30.6	42 6	31 1
22	culture 19 days		4.9	25 5	26 0
23			Nil	Nil	Nil

$P=$ * <0 05
† <0 01
‡ <0.005
§ <0 001

[1] Cells were exposed to hormone for 24 h and ^{75}SeM for 48 h

Table 3 Percentage Inhibition of ^{75}SeM Uptake by *in vitro* Exposure to Adriamycin†

Patient no	*Conc µg/ml*		
	1 0	5 0	10.0
11		89.0*	
12	9 0		65.0*
13	90 0*	95 0*	95 0*
15	70 0*	55.0*	39 0*
16	71 0*	93 0*	97 0*
17	57 0*	96.0*	98 0*

* $P=<0.001$

† Cells were exposed to drug for 24 h and ^{75}SeM for 48 h

Table 4 Percentage Inhibition of ^{75}SeM Uptake by *in vitro* Exposure to Novantrone

Patient no	*Conc µg/ml*			
	0 1	1.0	5.0	10 0
12	1 0	Nil		33 0†
13		80 0‡	97 0‡	97 0‡
14		15.0*	5 0	17 0*
15		14.0	48 0‡	52.0‡
16		77.0‡	94.0‡	98.0‡
17		81 0‡	97.0‡	97 0‡
18		61 2‡	90.3‡	88.1‡
19		74 4‡	93 7‡	92 7‡
20	13 2	55 4‡		48 6‡
21	52 7	57 5*		90.3†
22		13 2	2 9	23 1
23		Nil	20 8	39.6*

*$P=<0.05$ †$P=<0$ 005 ‡$P=<0.001$

Table 5 Percentage Inhibition of ^{75}SeM Uptake by *in vitro* Exposure to Vinblastine

Patient no	*Conc µg/ml*			
	1 0	5 0		10 0
1				Nil
2				16.0*
3				Nil
4				69 0†
5				Nil
7				1 0
8				Nil
9				74 0†
10				Nil
			Culture 8 days	Nil
11				42 0†
12	11 0			2 0
13	56.0†	53 0†		53 0†

*$P=<0$ 005 †$P=<0$ 001

carcinoma using Novantrone. They obtained 1 partial remission which lasted for 13 months. Further studies on the use of Novantrone in the treatment of metastatic renal carcinoma may therefore be of value.

Our results indicated that Adriamycin and the related drug Novantrone were more effective than other agents in inhibiting renal carcinoma cells *in vitro*. All patients whose tumours showed *in vitro* sensitivity to Adriamycin had extension of their disease beyond the kidney. The same was true for Novantrone and, by contrast, 3 of 4 patients whose carcinoma cells were not sensitive had tumours confined to the kidney. The spread of renal carcinoma cells beyond the kidney may be associated with a higher mitotic rate and thus with an increased sensitivity to Adriamycin or Novantrone. Support for this hypothesis comes from the observation that respectively 3 of 4 and 6 of 7 sensitive tumours showed a mixed cell pattern and/or moderate or poor differentiation.

Table 6 Percentage Inhibition of ^{75}SeM Uptake by *in vitro* Exposure to Methotrexate

Patient no.	*100*	*200*	*Conc µg/ml*	*400*
1				Nil
2				59.0*
3				Nil
4				55.0*
7				52.0*
8				Nil
9				83.0*
10			culture 8 days	12.0
11				5.0*
12	Nil	Nil		Nil
14	2.0	Nil		Nil
16	Nil	Nil		
17	2.5	55.0*		57.0*

* $P = < 0.001$.

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Maximum and Average Urine Flow Rates in Normal Male and Female Populations—the Liverpool Nomograms

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Summary—The study of voiding in men and women has been handicapped by the lack of a normal reference range covering urinary flow rates over a wide range of voided volumes.

Normal volunteers (331 males and 249 females) were studied. Each voided once into a calibrated Dantec Urodyn 1000 mictiograph. On a second occasion 282 men and 46 women voided. The maximum and average urine flow rates of the first voids in both sexes were compared with the respective voided volumes.

Nomogram charts, in centile form, for both the maximum and average urine flow rates were constructed using statistical transformations of the data. Males showed a significant decline in both urinary flow rates with age, although there was no statistically significant variation in either urine flow rate with respect to first versus repeated voiding. Females showed no statistically significant variation in either urine flow rate with respect to age, parity or first versus repeated voiding.

The maximum and average urine flow rates in both sexes showed an equally strong relationship to voided volume. No artificial restriction of voided volume, *e.g.* minimum 200 ml, appeared appropriate. These nomograms offer reference ranges for both maximum and average urinary flow rates in both sexes covering a wide range of voided volumes (15–600 ml).

The clinical usefulness of urinary flow rates has been attenuated by the lack of absolute values defining normal limits (Marshall *et al.*, 1983). As urinary flow rates are dependent on voided volume (Drake, 1948; Drach *et al.*, 1979a), these normal limits need to cover a wide range of voided volumes. Ideally, these should be in the form of nomograms.

The maximum and average urine flow rates are defined by the International Continence Society (Bates *et al.*, 1977) and are those rates most useful clinically. The lower limits of normal are still unclear in both sexes. Recommended values for the lower limit of normal for the maximum urine flow rate in men range between 15 (Holm, 1962) and 20 ml/s (Kaufman, 1957); in women the values range between 12 (Massey and Abrams, 1988) and 20 ml/s (Fantl *et al.*, 1982). A minimum rate of 15 ml/s is usually quoted if at least 200 ml have been voided (Farrar *et al.*, 1976; Whitfield, 1985).

Torrens and Morrison (1987), in a review of uroflowmetry, criticised the nomograms of von Garrelts (1957) in men and Backman (1965) in women for their insufficient data and inadequate allowance for reduced scatter at the lower voided volumes. Siroky *et al.* (1979) constructed nomograms using data from a relatively small number of younger men. The nomograms of Jorgensen *et al.* (1985) and Kadow *et al.* (1985) were restricted to older men.

The aim of this study was to establish normal reference ranges in both sexes, for the maximum and average urine flow rates, over a wide range of voided volumes and in the form of nomogram charts.

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Patients and Methods

A series of 331 male volunteers (aged 16–64 years) and 249 female volunteers (aged 16–63) were deemed normal for the study. They denied previous bladder surgery (including cystoscopy) and any of the following symptoms of voiding difficulty: hesitancy, poor stream, need to strain to void, sense of incomplete emptying and the need to revoid immediately. The females also denied any urinary incontinence and the males denied the additional symptom of urgency and a history of more than 1 urinary tract infection.

All of the males were production workers in a large motor vehicle plant. Approximately 80% of the women were hospital staff and visitors; the remainder were women attending an out-patient infertility clinic. A further 85 male and 97 female volunteers with positive urinary symptomatology were excluded from further study.

All voiding studies were performed in a completely private uroflowmetry room/toilet, lockable from the inside and outwith the hearing range of other staff and volunteers: A Urodyn 1000 mictiograph (Dantec, Denmark) was used. This machine uses the well evaluated (Rowan *et al.*, 1977) spinning-disk principle. It is compact, quiet and non-distracting in operation, with auto-start and stop facilities to remove any involvement of either staff or volunteers during the actual voiding studies.

Calibration was initially performed using the internal self-calibration programme on the apparatus and repeated at intervals to ensure consistency. Objective checking of the reading of voided volume, flow time and average flow rate was performed using known fluid volumes and time (stopwatch). Overall error of the average flow rate lay within the ±1 to 3% limit quoted by the manufacturer and well within the 5% limit acceptable to the International Continence Society (Rowan *et al.*, 1987).

Volunteers were encouraged to attend with a full bladder. Each voided at least once; 282 men and 46 women voided on a second occasion. All studies were free flowmetry voids.

The maximum flow rate, average flow rate and voided volume were measured. If voiding was interrupted, the period(s) of interruption were excluded when calculating the flow time. All flow rates and times produced by the uroflowmeter's computer were checked manually against the flow curve.

Maximum and average flow rates from the first voids of the 331 men and 249 women were compared with their respective voided volumes.

In order to establish nomograms of 1 variable allowing for a relationship with a second variable, it was necessary to estimate both the form for the relationship and the variability inherent in that relationship. This was most easily achieved by a statistical transformation of the data such that the 2 variables then showed a linear relationship and an approximately normal variance about that relationship.

Having assumed a form for the relationships between maximum and average urinary flow rates and the voided volume, we used standard multiple regression techniques to assess the possible effects of age in both sexes and parity in the women. Similarly, for the 282 men and 46 women who voided on a second occasion, it was possible to look for any systematic effect between voids.

For presentation, the nomograms have been expressed in centile form and transformed back to their original scales, giving a curvilinear appearance. The nomograms were produced using the SAS graphic package on an IBM 3083 computer (SAS, 1985).

Results

The median voided volumes in the first voids were 195 ml (men) and 171 ml (women).

The median age of the men was 49 years (range 16–64). The median age for the women was 32 years (range 16–63); 70% of the women were nulliparous, 10% and 14% had 1 and 2 children respectively, whilst 6% had more than 2 children.

The men showed a decline in both urinary flow rates with increasing age after allowing for voided volume. This decline was approximately 1.0 to 1.6 ml/s/10 years (maximum) and 0.6 to 1.0 ml/s/10 years (average). The women showed no dependence of either flow rate on either age or parity. Paired analysis showed no systematic difference in either sex between the first and second voids with regard to either flow rate.

In men, equations for the nomograms related flow rates with both voided volume and age. These became:

(a) $$\sqrt{(\text{Maximum flow rate})} = 2.37 + 0.18 \times \sqrt{(\text{voided volume})} - 0.014 \times \text{age}$$

Root mean square error: 0.727

(b) $$\sqrt{(\text{Average flow rate})} = 1.80 + 0.14 \times \sqrt{(\text{voided volume})} - 0.011 \times \text{age}$$

Root mean square error: 0.535

The ages of 35 and 60 were selected as representative median points for men under 50 years and men 50 years and over, respectively.

In women, it was unnecessary to subclassify the data on the basis of either age or parity. The final equations for the nomogram graphs were then:

(a) Ln (maximum flow rate)

$$= 0.511 + 0.505 \times \text{Ln (voided volume)}$$

Root mean square error $= 0.340$

(b) Square root (average flow rate)

$$= -0.921 + 0.869 \times \text{Ln (voided volume)}$$

Root mean square error $= 0.640$

Figures 1 and 2 show the Liverpool nomograms for the maximum and average urine flow rates respectively for men under 50 years. Figures 3 and 4 show the Liverpool nomograms for the maximum and average urine flow rates respectively for men 50 years and over. Figures 5 and 6 show the Liverpool nomograms for the maximum and average urine flow rates in women.

Both flow rates showed an equally strong relationship with voided volume in both sexes. The data sets for the studies in both sexes allowed estimation of centiles for both flow rates in the range 15 to 600 ml.

Figure 7 shows the data set for the maximum urine flow rate (men 50 years and over) superimposed on the respective nomogram. Figure 8 shows the data set for the average urine flow rate in women superimposed on the respective nomogram. These figures demonstrate the ability of the different nomograms to fit the data sets.

Figure 9 shows maximum urine flow rates from a large number of voids in one 35-year-old male volunteer, superimposed on the nomogram chart.

Discussion

These nomograms were constructed to provide normal reference ranges in both sexes for urinary flow rates, covering a wide range of voided volumes and in centile form. Nomograms in centile form have been found to be easily interpretable in some obstetric and paediatric situations (Chamberlain *et al.*, 1975, Hensinger, 1976). The use of statistical transformations in their construction overcame the problems created by inaccuracy when untransformed standard deviations are used (Backman, 1965; Susset *et al.*, 1973; Siroky *et al.*, 1979; Fantl *et al.*, 1982). The data, especially for the maximum urine flow rate in women, have a greater scatter above the line of the mean. The use of untrans-

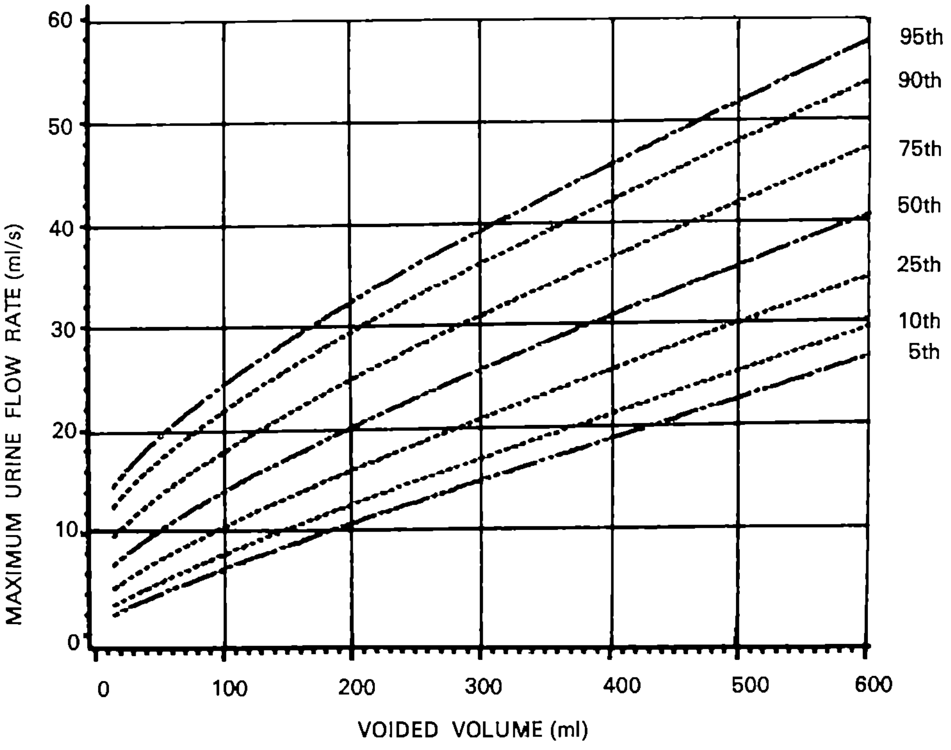

Fig. 1 Liverpool nomogram for maximum urine flow rate (men under 50 years · median 35).

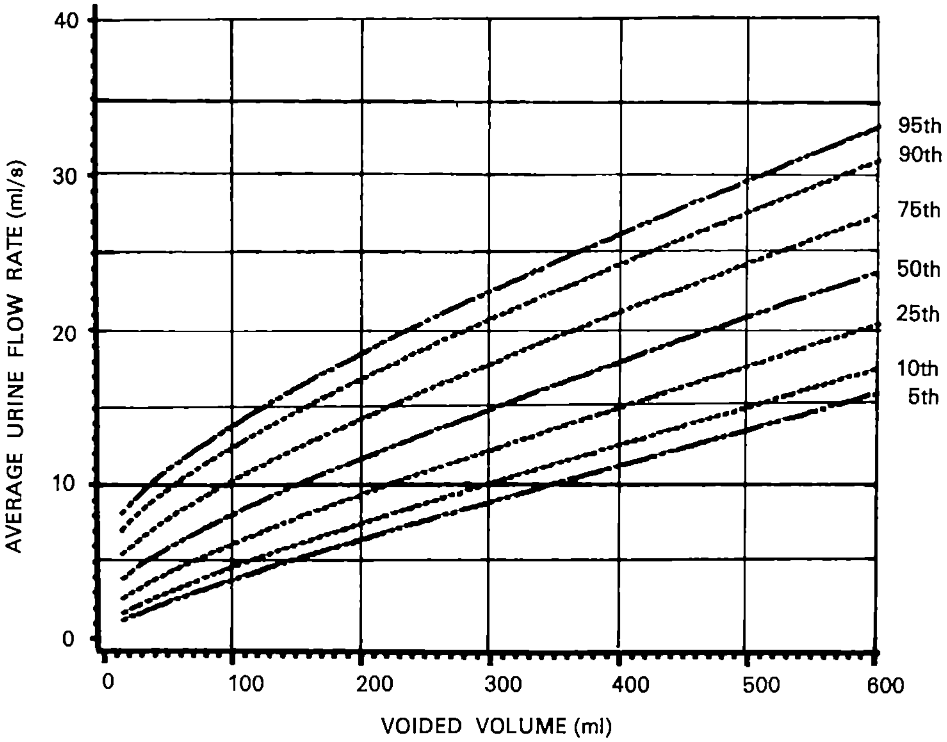

Fig. 2 Liverpool nomogram for average urine flow rate (men under 50 years · median 35)

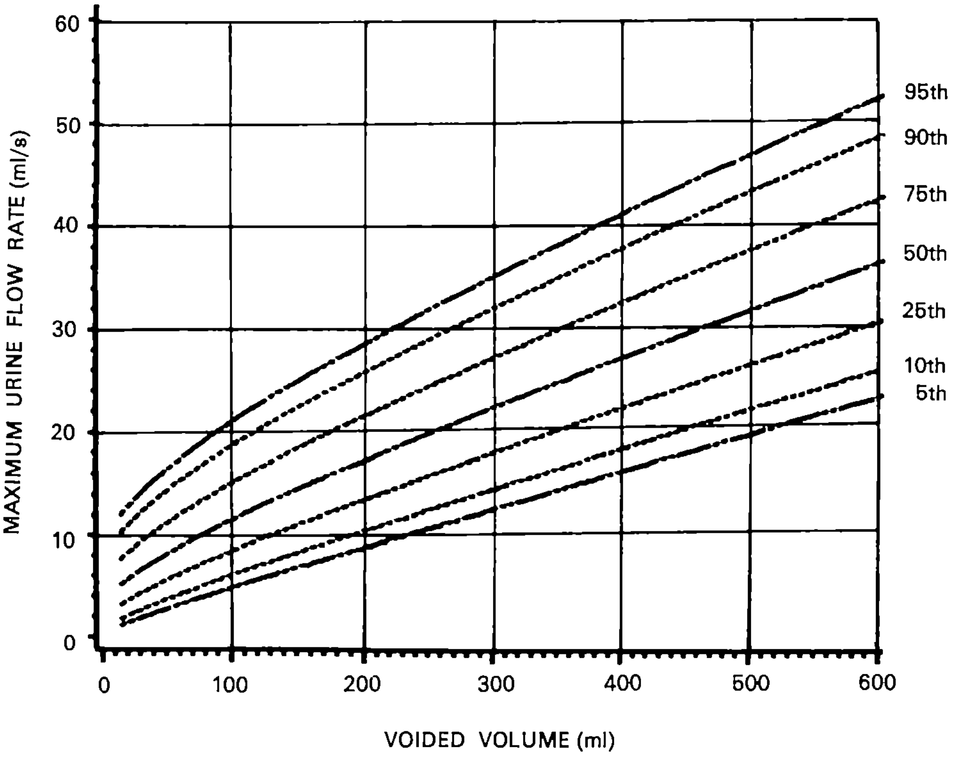

Fig. 3 Liverpool nomogram for maximum urine flow rate (men 50 years and over: median 60)

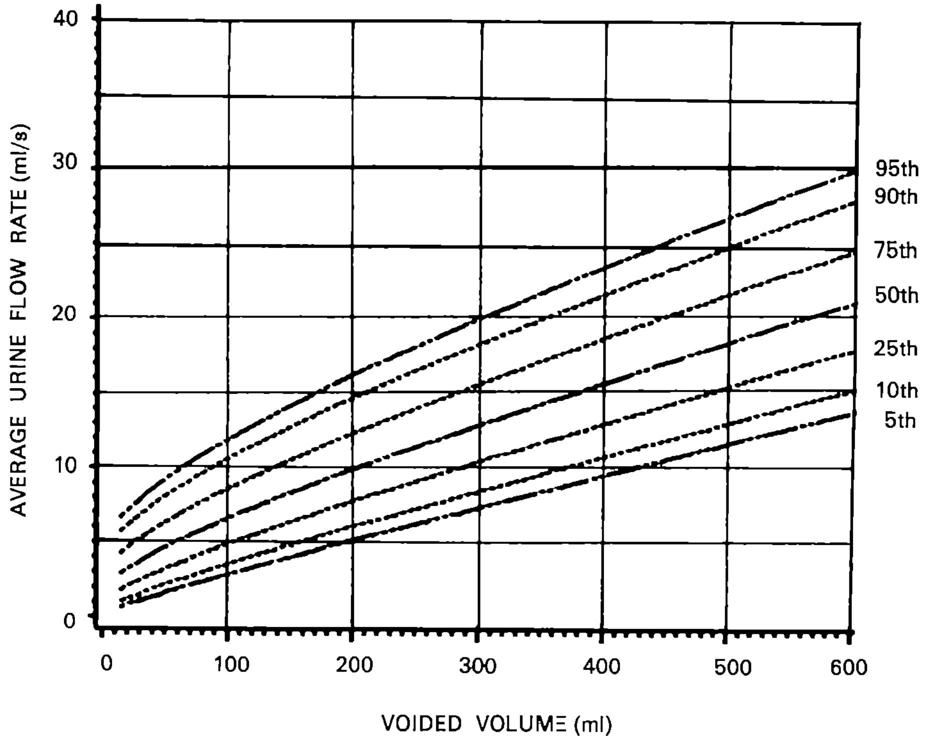

Fig. 4 Liverpool nomogram for average urine flow rate (men 50 years and over median 60)

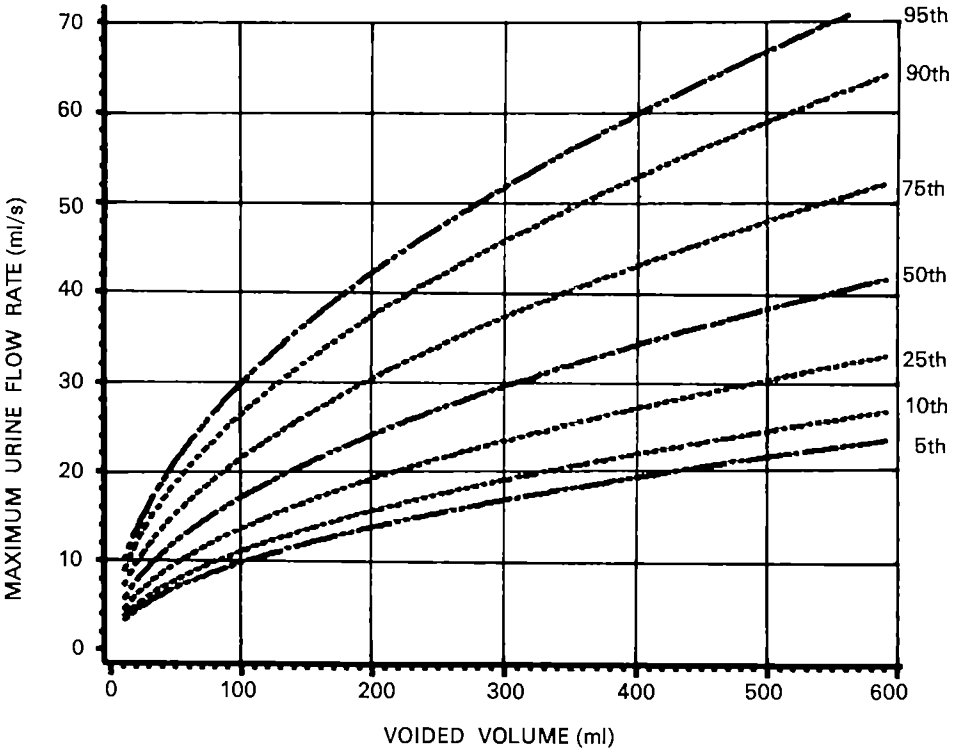

Fig. 5 Liverpool nomogram for maximum urine flow rate in women.

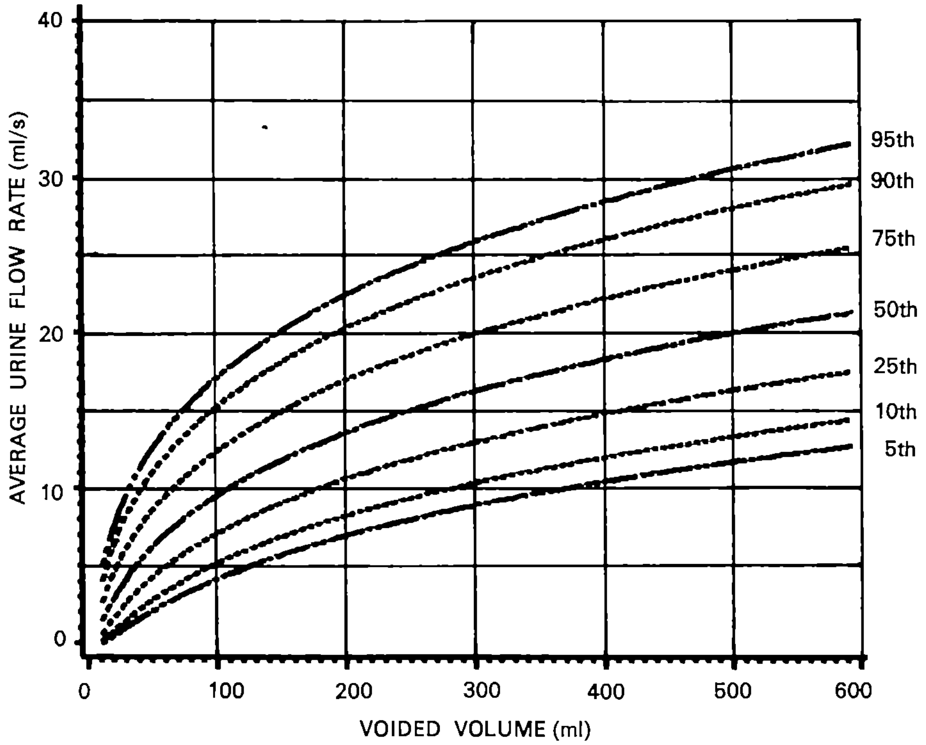

Fig. 6 Liverpool nomogram for average urine flow rate in women.

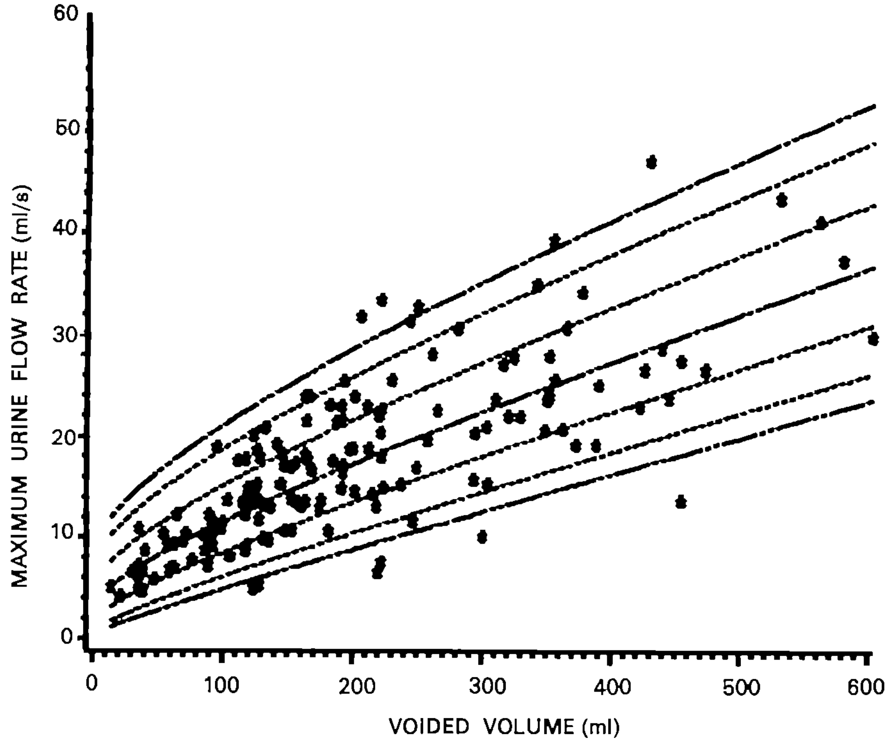

Fig. 7 Maximum urine flow rate nomogram (men 50 years and over: median 60) with the data set used in its construction superimposed

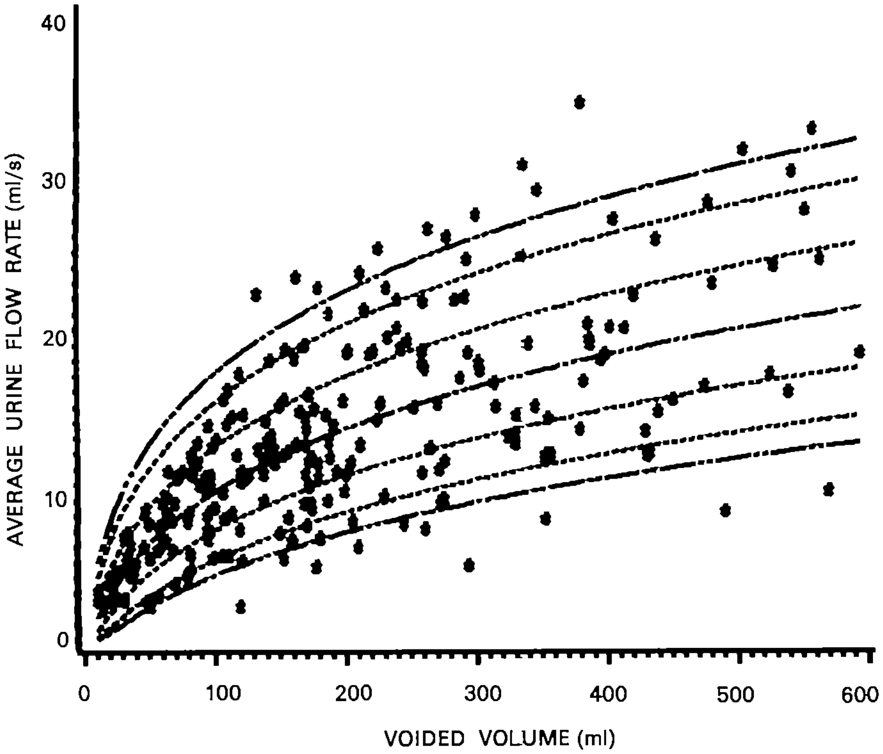

Fig. 8 Average urine flow rate nomogram in women with the data set used in its construction superimposed.

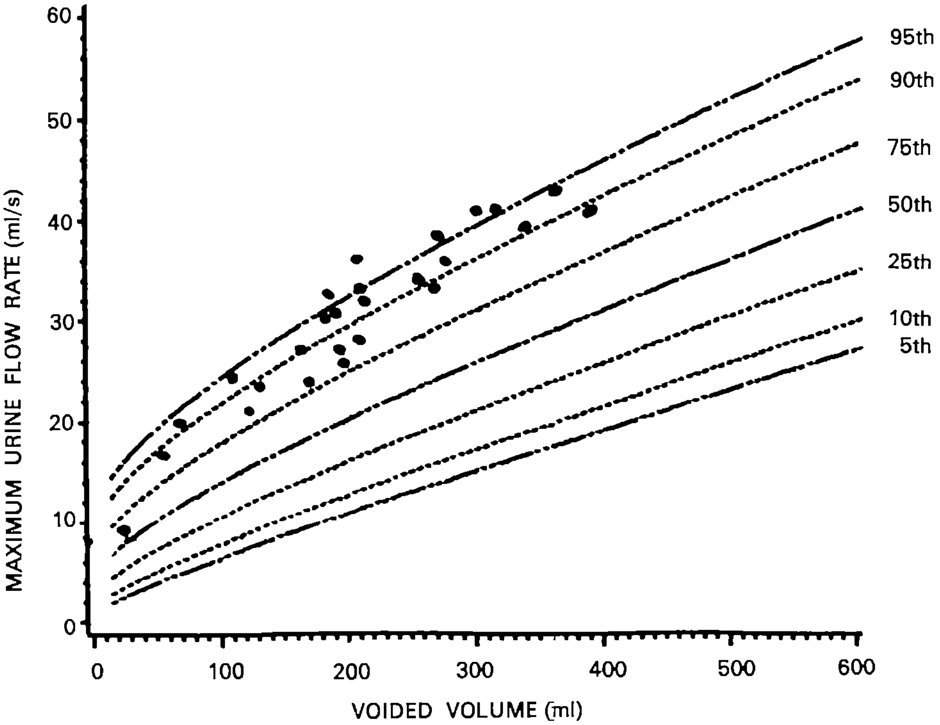

Fig. 9 Maximum urine flow rates from a large number of voids by 35-year-old male volunteer superimposed on the nomogram chart

formed standard deviations could easily create excessively low limits for standard deviations below the mean.

The use of nomograms overcomes the dangers of referencing flow rates to any one voided volume. A maximum urine flow rate of 11 ml/s in men, or 15 ml/s in women, might fall just inside the fifth centile curve at 200 ml voided volume, although well outside the same curve at 400 ml. The normality of these flow rates may be then interpreted quite differently at these 2 voided volumes.

Artificial restriction of voided volumes within the nomogram in either sex, *e.g.* to above 150 or 200 ml, appeared inappropriate from our investigations. Attempts have been made to develop linear relationships in men between the various flow rates both above 150 ml (Drach *et al.*, 1979b) and below 150 ml (Marshall *et al.*, 1983). As the median voided volumes in our series were 195 ml (men) and 171 ml (women), approximately half of the voided volumes would not be explained by either method. There may be practical difficulties in waiting for male or female patients to collect bladder volumes over 200 ml. In some pathological conditions, patients may be unable to hold 200 ml (Ryall and Marshall, 1982; Abrams, 1983). The only restriction of voided volumes in our series is the limits of the data set (15–600 ml).

The equally strong relationship between maximum and average urinary flow rates with voided volume in both sexes tends to suggest that the clinical use of either flow rate is equally valid. They are numerical representations of the same flow curve and tend to provide similar clinical information (Zinner, 1982). The centile rankings of the maximum and average urine flow rates are not, however, necessarily interchangeable in individual cases.

Both sexes showed a remarkable consistency in the centile rankings of the paired first and repeated voids. This was further witnessed in the multiple voids from the single 35-year-old male volunteer (Fig. 9) and the single 25-year-old female volunteer. There is, therefore, a need for data from a large number of normal volunteers in the construction of such nomograms, rather than multiple voids from a small number of patients (Susset *et al.*, 1973; Fantl *et al.*, 1982; Rollema *et al.*, 1985). It can be concluded that in the majority of normal men and women, the centile rankings of successive voids will not differ widely. However further studies are necessary in order to justify the same conclusion in men and women with lower urinary tract dysfunction.

The previously suggested deterioration in male urinary flow rates with age (von Garrelts, 1957; Torrens, 1987) has been confirmed in this study. Ideally, 10-year age groupings would allow increased statistical accuracy within the nomogram charts. In clinical terms, a large number of nomograms might prove rather confusing.

Our results support the view of most authors that in women there is no significant dependence of urinary flow rates on age (Drach *et al.*, 1979a; Fantl *et al.*, 1982). The study of Torrens and Kavanagh (1987), supporting the opposite view, was not performed on asymptomatic women. Our finding of no significant effect of parity on flow rates in normal women supported the findings of Drach *et al.* (1979a) and Fantl (1982).

No systematic deterioration of either flow rate in either sex was discernible at higher voided volumes, as previously observed in men (Drach *et al.*, 1979a; Ryall and Marshall, 1982; Abrams *et al.*, 1983).

These charts are offered as providing easily interpreted normal reference ranges in both sexes, for the 2 most commonly used urinary flow rates, over a wide range of voided volumes. Further studies are now under way to compare centile rankings of the flow rates of men and women at higher risk of voiding difficulties, and other lower urinary tract disorders, with the results of the normal men and women contained herein.

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Interstitial Cystitis and the Urethral Syndrome: a Possible Answer

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Summary—A study was made of 20 patients fulfilling the criteria customarily used for the diagnosis of interstitial cystitis. A possible infective aetiology was sought by culture of bladder tissue, catheter and midstream specimens of urine, and urethral swabs by methods capable of detecting fastidious bacteria as well as aerobic pathogens. All bladder biopsies showed the histological appearances usually associated with interstitial cystitis, and bacteria were isolated from the catheter specimens and/or bladder biopsies of 12 patients. Eight of these isolates were fastidious bacteria, *Gardnerella vaginalis* (6) and *Lactobacillus* sp. (2). Fastidious bacteria were isolated from the midstream specimen of urine (MSU) and/or urethral swab of 6 other patients. The correlation of the histological and bacteriological findings supports the hypothesis of an infective aetiology and suggests that the so-called urethral syndrome and interstitial cystitis may be the earlier and later stages of the same disease process. The importance of early diagnosis of infection in these patients is emphasised.

Interstitial cystitis is an ill defined condition for which no cause has been found and no effective therapy developed (Lancet, 1985; Messing, 1987). The diagnosis is usually made if a patient with persistent urinary symptoms has cystoscopic appearances and bladder histology suggesting chronic inflammatory change but the urine, although often showing pyuria, yields no growth on culture (Lancet, 1985). In advanced cases of the disease deep ulcers, first described by Hunner (1915), are present. Therapy has varied from hydrostatic dilatation to steroids, but has generally been unsatisfactory; the symptoms have become so severe in some patients as to necessitate cystectomy (Webster and Galloway, 1987).

The probability that a condition characterised by chronic inflammatory change is due to infection prompted us to develop two recent lines of research in seeking an infective cause. Elliott *et al.* (1985) demonstrated, by scanning electron microscopy and culture of bladder biopsies, that organisms may be embedded in the bladder wall but not detected by urine culture. Secondly, it has been shown by many workers that if appropriate culture media and prolonged incubation in an atmosphere containing CO_2 are used, many fastidious species of bacteria not detectable by conventional techniques can be isolated from urine. This work has recently been reviewed (Maskell, 1986).

A search for fastidious bacteria in the urine of patients with interstitial cystitis has never before been made. Using appropriate bacteriological techniques, cystoscopy and bladder biopsy, we studied patients with persistent lower urinary tract symptoms associated with repeated urine cultures which yielded no growth when conventional culture methods were applied.

Patients and Methods

Men and women between 16 and 70 years of age with longstanding and unremitting urinary symptoms ($\geqslant 1$ year) for which no infective cause had been identified by standard bacteriological techniques were eligible for inclusion. These were patients who would normally be considered for

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cystoscopy as part of their diagnostic evaluation. Patients must have had at least 3 negative MSUs whilst off antibiotic therapy within the preceding 6 months. In reviewing the results of previous MSU specimens a negative result was taken to mean $<10^4$ organisms/ml after overnight culture on cysteine lactose electrolyte deficient (CLED) medium. Patients were withdrawn from the study if they received antibiotics between attending Outpatients and their planned day-case admission for cystoscopy or if urine specimens collected on the day of investigation contained antibacterial substances.

Comprehensive clinical data were collected on every patient. Special reference was made to urinary symptoms, past antibiotic therapies and their effectiveness, and a history of previous urogenital surgery or disease. All urine culture results in the preceding 4 years were examined by scrutinising the patients' case notes and laboratory records. Three consecutive early morning urines (EMUs) were collected for mycobacterial culture as an outpatient. Cystoscopy was performed under general anaesthesia as a day-case. A pre-cystoscopy MSU was collected from the patient on arrival and refrigerated at 4°C until examination. After induction of anaesthesia, the external genitalia (including the urethral orifice) were cleansed with sterile water and a urethral swab taken and placed in Stuart's transport medium. Palpation *per vaginam* for induration of para-urethral tissues was then carried out. A standard 21F cystoscope was introduced and a midstream catheter specimen of urine (CSU) obtained. The bladder appearance before and after distension with sterile water and the bladder capacity were recorded. Five standard rigid cup biopsies of the bladder wall were taken and the resultant ulcers fulgurated.

Microscopy was performed on 60 µl of uncentrifuged urine under an inverted microscope (Maskell, 1982). The pre-cystoscopic MSU, urethral swab, CSU and 1 bladder biopsy specimen were examined by inoculation on to CLED agar, blood agar and chocolated blood agar for incubation in air supplemented with 7% carbon dioxide, and on to blood agar for anaerobic incubation. Another bladder biopsy specimen was placed into thioglycollate medium immediately after collection and the broth and biopsy then subcultured on to the above media after 24 h. Biopsies were ground up using a Griffith's tube before inoculation on to media. Direct and subculture plates were kept for 72 h. Organisms were identified using standard bacteriological techniques, including speciation of all isolates by conventional and API methodology. The pre-cystoscopic MSU and CSU were examined for antibacterial substances by using a *Bacillus subtilis* spore plate bioassay.

Three consecutive early morning urines were cultured for mycobacteria using standard methods. One bladder biopsy was placed in selective Kirchner's medium, incubated for 5 weeks and then subcultured on to Lowenstein-Jensen, pyruvic egg and Middlebrook 7H11 media. All media were incubated at 37°C and examined weekly for 12 weeks.

One bladder biopsy was processed for examination using a scanning electron microscope (JEOL 35c). A further biopsy specimen was submitted for routine histological examination, the pathologist being unaware of the clinical and endoscopic findings.

Results

Twenty-one patients fulfilled the admission criteria for the study; 1 patient was excluded because of the finding of antibacterial substances in her urine, leaving 20 patients for analysis, of whom 19 were female. No patient was identified as having tuberculous cystitis. In order to place our findings in the context of the currently accepted clinical syndromes, and to assess their significance, a clinical diagnosis of "interstitial cystitis" (IC), "bacterial cystitis" (BC) or "urethral syndrome" (US) was made for each patient on the following basis. IC was diagnosed when, in the absence of aerobic bacteria in the bladder urine, cystoscopy revealed pinpoint telangiectases, haemorrhage, or ulceration of the vesical mucosa after hydrodistension of the bladder (Messing, 1987). BC was diagnosed when aerobic urinary pathogens were isolated from the bladder urine. US was diagnosed when the cystoscopic appearances of the bladder mucosa were normal and aerobic pathogens were not isolated from the bladder urine (MRC Bacteriuria Committee, 1979). Using these criteria, 10 patients (50%) were deemed to have IC, 4 (20%) to have BC and 6 (30%) to have US. The 4 patients with BC were infected with *Escherichia coli* (2), *Proteus mirabilis* (1) and Group B streptococcus (1). Comparison of the clinical features in the 3 groups revealed that the patients with US were younger and the duration of their symptoms was shorter (Table 1). Otherwise, no significant differences in the frequency or severity of symptoms between the groups could be identified. Eleven patients had had a previous cystoscopy and 7 had undergone urodyn-

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Table 1 Comparison of Clinical Features

	Interstitial cystitis (n=10)	*Bacterial cystitis (n=4)*	*Urethral syndrome (n=6)*
Age (years)	51 0 (26–79)	63 0 (57–67)	38 0 (25–55)
Sex (female) (%)	10 (100)	4 (100)	5 (83)
Duration of symptoms (years)	7.4	3 3	2 3
Frequency (x/16h)	20 7	17 5	14 3
Nocturia (x/8h)	3 3	2 8	3 8
Urgency (%)	8 (80)	3 (75)	3 (50)
Incontinence (%)	3 (30)	0	2 (33)
Hesitancy (%)	3 (30)	0	1 (17)
Haematuria (%)	1 (10)	0	1 (17)
Pain · suprapubic (%)	7 (70)	2 (50)	4 (67)
perineal (%)	2 (20)	1 (25)	1 (17)
urethral (%)	1 (10)	1 (25)	2 (33)
Previous UTIs with aerobic pathogens (%)	7 (70)	1 (25)	4 (67)
Responsiveness to antibiotics (%)	0	2 (50)	2 (33)
Previous cystoscopy (%)	6 (60)	3 (75)	2 (33)
urodynamics (%)	3 (30)	3 (75)	1 (17)
genitourinary surgery (%)	2 (20)	0	1 (17)

Table 2 Correlation between Clinical Diagnosis, Endoscopic Appearance and Presence or Absence of Fastidious Bacteria in the Bladder

	Interstitial cystitis (n=10)	*Bacterial cystitis (n=4)*	*Urethral syndrome (n=6)*
Urethral induration	6	2	2
Endoscopy appearance			
Normal	—	1	6
Telangiectatic	5	1	—
Haemorrhagic	4	2	—
Ulcerated	1	—	—
Capacity <450 ml	4	—	—
Bladder infection with fastidious bacteria			
CSU and biopsy culture	5 } (70%)	0	1 } (17%)
CSU only	2 }	0	0 }

amic studies. Again, there were no significant differences in the frequency with which past genitourinary instrumentation or surgery had been performed. No patient had a past history of sexually transmitted disease.

Documented evidence of a past urinary tract infection with a conventional urinary pathogen in the preceding 4 years was found in 70% of patients with IC and this was also true of patients with US (67%). All patients had received at least 1 course of antibiotics in the past, several of them many. None of the 10 patients with IC reported any benefit from antibiotics, although of the patients with either BC or US, 40% had previously responded.

On palpation *per vaginam*, half of the patients were found to have indurated para-urethral tissues. The cystoscopic findings are detailed in Table 2 and they are correlated with the presence of bladder infection with fastidious organisms. By definition, all patients with IC had an abnormal appearance of their bladder mucosa, whereas all patients with US had a normal appearance. Only 1 patient with IC had the characteristic Hunner's ulcer: 4 of the 10 patients with IC had a contracted bladder (capacity <450 ml). Of the 4 patients with BC, 3 had the cystoscopic appearances found in IC. Pyuria (>10 white cells/µl) was present in the bladder urine or 50% of those with BC, 30% of those with IC and 33% of those with US.

The full bacteriological results, including the isolations of fastidious organisms, are given in Table 3. In 6 patients (5 with a diagnosis of IC), organisms were grown from the bladder biopsies. In every case, identical organisms were recovered from the cystoscopic and midstream specimens of urine. *Gardnerella vaginalis* was isolated in 5 of these cases and *Lactobacillus* sp. in 1. In 1 of these patients, bacilli were visible on the mucosal surface by scanning electron microscopy. In 6 patients, bacteria were isolated from bladder urine at cystoscopy but not from the bladder wall: 4 isolates were conventional urinary pathogens (detailed above) and 2 were fastidious species (*G. vaginalis* (1), *Lactobacillus* sp. (1)). Of the remaining 8 patients, 4 had a growth of at least 10^4 organisms/ml of either *G. vaginalis* (3) or *Lactobacillus* sp. (1) in their MSU with a heavy and predominant growth of the same organism from their urethral swab, and 4 had sterile urine with a predominant growth of *Lactobacillus* sp. (2) or *Proteus* sp. (2) in their urethral swab.

Examination of bladder biopsies by routine histological techniques revealed a remarkably homogeneous group. The biopsies from all patients showed a mildly oedematous and hyperaemic mucosa, mild to moderate submucosal oedema and a mild to moderate chronic inflammatory cell infiltrate. Two biopsies revealed an excess of mast cells: 1 from a patient with BC and the other from a patient with US. In all cases the results of the histological examination were deemed by the pathologist to be consistent with the non-specific changes described in interstitial cystitis.

Discussion

A striking feature of these findings was that there were no significant differences in the type or severity of symptoms in the patients allotted to the different clinical diagnoses, although those deemed to have IC were older and had suffered longer than those deemed to have US. Furthermore, the bladder biopsies from all patients, including those with normal cystoscopic appearances, showed non-specific inflammatory changes consistent with those normally thought to indicate IC. Tait *et al.* (1985) reported similar histological changes in the bladder mucosa of women with US. These data strongly suggest that the patients in our study, rather than suffering from quite separate diseases, showed the characteristics of different stages of the same disease—an inflammatory process probably beginning in the urethra and extending over the course of time to the para-urethral tissues and the bladder, eventually resulting in deep-seated infection of the bladder wall and the characteristic cystoscopic appearances of IC. This hypothesis is supported not only by the histological findings but by the presence of pyuria in the bladder urine of 33% of the patients deemed to have US. This finding agrees with that of Stamm *et al.* (1980).

There are several problems in assessing the relationship of the bacteriological findings to the disease process. The diagnosis of IC is customarily made in patients with severe symptoms and cystoscopic and histological evidence of chronic bladder inflammation, but with negative conventional aerobic urine culture. Had urine culture yielded aerobic bacteria the condition would probably have been regarded as chronic bacterial cystitis. Now that we have demonstrated the presence of fastidious bacteria in bladder urine and tissue of many of these patients it would seem logical to accept a pathogenic role for these organisms in this chronic inflammatory condition. The consistency of isolation of the same bacterial species from different levels of the urinary tract in individual patients supports the hypothesis that there is a single disease process in which fastidious bacteria play an important part. It is likely that aerobic urinary pathogens are also concerned in the natural history of the condition. The finding of such organisms in the bladder urine of 4 of our patients, all of whom fulfilled the criterion for inclusion in the study of at least 3 negative MSU specimens within the previous 6 months, and 3 of whom showed the cystoscopic appearances of IC, together with the history of proven infection with such organisms in 70% of our patients, suggests that they may play a primary (and possibly recurrent) role. It is well documented that BC and US commonly coexist in the same patient and that fastidious organisms are present in large numbers in the urine of patients with US (Maskell *et al.*, 1983). There are data to support the hypothesis that these organisms acquire a pathogenic role as a result of repeated antibacterial treatment given for urinary symptoms (Maskell, 1986). The isolation of only fastidious bacteria, most commonly *G. vaginalis*, from the bladder tissue of our patients may be an indication of favourable conditions for their survival in damaged tissue and the fact that, unlike the aerobic pathogens, they are not susceptible to many of the antibacterial agents used to treat urinary symptoms. Evidence which supports our hypothesis of the progression of infection from the urethra and para-urethral tissues to the bladder has recently been presented by Fihn *et al.* (1988), although only aerobes were sought in their study.

Table 3 Complete Bacteriological Findings

Biopsy of bladder	*Cystoscopy (CSU)*	*MSU*	*No of patients*	*Organisms*
+	+	+	6	*G. vaginalis* (5) *Lactobacillus* sp. (1)
–	+	+	6	*E. coli* (2) *Proteus mirabilis* (1) GpB streptococcus (1) *G vaginalis* (1) *Lactobacillus* sp. (1)
–	–	+	4*	*G. vaginalis* (3) *Lactobacillus* sp (1)
–	–	–	4**	

* Predominant organism isolated from urethral swab identical

** Urethral swab *Proteus* sp (2), *Lactobacillus* sp (2)

Should this hypothesis be correct, the difficulty of obtaining control data is immediately apparent. It would be unethical to submit women not subject to urinary symptoms to cystoscopy and bladder biopsy. If cystoscopy were performed, for control purposes, on women subject to urinary symptoms at a time when they were symptom-free, it is possible that they might be at various stages of the natural history of the disease that we are describing, and therefore show bacteriological findings similar to those of our patients. It has been shown that fastidious organisms are isolated significantly more often from the urine of women who suffer from US at times when they are symptom-free between attacks than from women who do not suffer from dysuria and frequency (Maskell *et al.*, 1983). Men, who are more often cystoscoped than women for reasons other than urinary symptoms, would not have provided valid control data for a study in which 19 of 20 patients were women. In the absence of specific controls, therefore, support for the significance of our findings must be sought from other studies. There is no doubt that *G. vaginalis* can gain access to the bladder. McFadyen and Eykyn (1968) isolated it from suprapubic aspirates of a large number of pregnant women, a significantly higher percentage of whom subsequently developed urinary symptoms than that of women from whom it was not isolated. They also reported isolation of this organism from suprapubic aspirates from non-pregnant women with urinary symptoms and from urine collected by ureteric catheterisation from 1 patient. It has been recorded as causing acute pyelonephritis, Wilson and Barratt, 1986), perinephric abscess (Finkelhor *et al.*, 1981), haemorrhagic cystitis (Abercrombie *et al.*, 1978) and prostatitis (Patrick and Garnett, 1978). It has been recovered from 16% of patients with chronic kidney disease in one series (Fairley and Birch, 1983) and from 15% of renal transplant recipients (Birch *et al.*, 1981), suggesting an association with uroepithelial inflammation and damage. Our positive biopsy cultures and the fact that, on scanning electron microscopy, the bacteria were seen embedded in the vesical mucosa, albeit only in 1 of our patients (our failure to demonstrate it in the other 5 patients with positive biopsy cultures does not, of course, exclude its presence there), rule out the possibility that these organisms were innocent colonisers of the bladder urine or were introduced on the cystoscope. We have recently obtained further supporting evidence for the presence of these organisms in the urine of women undergoing urodynamic studies for urge incontinence and other urinary symptoms (Payne *et al.*, 1988). They were found in catheter specimens from over one-third of the patients and in midstream specimens from most of the remainder. Detrusor instability and urge incontinence are two other clinical diagnoses for which no primary cause has yet been identified; it seems reasonable that they might be consequences of urethral, para-urethral or bladder inflammation caused by fastidious organisms. In contrast to these findings, other workers, using suprapubic aspiration or catheterisation, have demonstrated that the presence of *G. vaginalis* or other fastidious bacteria in bladder urine is exceptional in healthy men or non-pregnant women (Birch *et al.*, 1981; Brumfitt *et al.*, 1981).

Whilst *Lactobacillus* sp. is the organism most commonly isolated from the urine of women with US (Maskell *et al.*, 1983), it was isolated from the bladder urine of only 2 of our patients, *G. vaginalis* being the commonest bladder isolate. US is very common, whereas IC is comparatively rare; it may be that those patients infected with *G. vaginalis* are more likely to progress to bladder involvement. The association of *G. vaginalis* with squamous epithelium is well known; since squamous metaplasia may occur at the trigone, often in association with aerobic urinary infection, the ability of *G. vaginalis* to adhere to such cells may provide an effective mechanism for this organism to extend further from the urethra to the bladder as a secondary pathogen. It has been demonstrated in experimental animal models that acute cystitis denudes the glycosaminoglycan mucin layer, which provides an important mechanism for protecting the epithelium against the ingress of bacteria (Balish *et al.*, 1985). When this layer is destroyed, or the epithelium loses the ability to produce it, the bladder mucosa is more susceptible to further bladder invasion. Bladder wall infection with less pathogenic species of bacteria could then follow and go undiagnosed and untreated if reliance is placed on traditional methods of urine culture.

In this diagnostic study we did not address the problem of treatment. We consider, however, that the complexity of the problem in patients in whom the disease process has advanced to the stage of deep-seated bladder inflammation makes it unlikely that antibacterial treatment directed at one organism will do more than allow its replacement with another. The best hope is likely to lie in the prevention of progession to the stage at which a clinical diagnosis of IC is made. If it is sought in urine by appropriate culture methods, *G. vaginalis* accounts for between 0.8 and 2.3% of urinary isolates (1% is the most recent figure in our laboratory) (Josephson and Thomason, 1986). Detection and appropriate antibacterial treatment at an early stage of the disease process probably offers the best hope of helping patients with this very troublesome condition.

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Identification of the Source of Haematuria by Automated Measurement of Red Cell Volume

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Summary—The mean corpuscular volume (MCV) of urinary erythrocytes was measured by a Coulter Counter in 42 patients with asymptomatic haematuria. All patients had the source of haematuria established by a renal biopsy, cystoscopy or radiology. The mean urine MCV was significantly less in those with glomerular disease (n = 21) than in those with non-glomerular haematuria (n = 21). In every patient with glomerulonephritis, urinary erythrocytes were smaller than those in their own venous blood. Conversely, urinary red cells larger than venous blood were confined to patients with a non-glomerular source. Coulter analysis of urine provides a simple and objective aid to the diagnosis of haematuria.

Asymptomatic microscopic and macroscopic haematuria is a common reason for referral to both nephrologists and urologists, and significant pathology is often found in the upper or lower urinary tract (Carson *et al.*, 1979; Golin and Howard, 1979). A variety of factors (proteinuria, patient's age, presence of urinary leukocytes or casts) may help to establish whether bleeding arises from a glomerular or non-glomerular source but none is completely reliable. Under the phase contrast microscope urinary erythrocytes from patients with glomerulonephritis are small and crenated (Fairley and Birch, 1982; Birch *et al.*, 1983). Conversely, urinary red cells from lesions in the renal collecting system and bladder are morphologically normal. However, others have found this technique difficult to reproduce (Venkat Raman *et al.*, 1986) and the aim of the present study was to establish whether measurement of MCV by a standard laboratory Coulter Counter could be used to provide a simple and objective indication of the source of haematuria.

Patients and Methods

A series of 42 consecutive patients was studied. They had presented for investigation of macroscopic or microscopic haematuria and the diagnosis was established by renal biopsy, cystoscopy or radiology. The range of diagnoses is shown in Table 1. An aliquot of a midstream urine sample was sent for culture and a further 20 ml were centrifuged at 1500 rpm for 5 min; 44.7 µl of the resulting sediment were suspended in Isoton and analysed for MCV on a Coulter S+III using the predilution mode. If erythrocyte numbers were insufficient to produce a smooth frequency distribution curve, a further 44.7 µl of sediment were added.

The original urine sample was analysed immediately after voiding in all patients and after having remained overnight at room temperature in 22 patients. Haematuria was semi-quantified by Labstix testing (Ames Laboratories Ltd) at the time of analysis and ranged from + to +++. A venous blood sample was taken for comparison with urine.

Statistical analysis was by Wilcoxon rank sum test. Means are given with standard deviations.

Results

No patient had urinary tract infection. Individual values of urinary erythrocyte MCV in the 2 groups of patients are shown in Figure 1; 18 patients with glomerulonephritis had urinary cells below 80 fl, the lower normal range for blood erythrocytes. In contrast, the urinary cells of 18 patients with non-

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Table 1 Diagnoses in the 2 Groups of Patients

Glomerular	*No of patients*	*Non-glomerular*	*No of patients*
IgA (Berger's) nephropathy	7	Bladder carcinoma	11
Henoch-Schonlein nephritis	5	Renal stone	2
Mesangiocapillary glomerulonephritis	2	Prostatic carcinoma	2
Polyarteritis nodosa	2	Chronic cystitis	1
Lupus nephritis	1	Radiation cystitis	1
Alport's syndrome	1	Renal trauma	1
Thin membrane disease	1	Coagulopathy	1
Focal glomerulosclerosis	1	Renal carcinoma	1
Idiopathic crescentic nephritis	1	Papillary necrosis	1
Total	21	Total	21

glomerular bleeding were of normal size or larger. Urinary red cells >98 fl (upper limit of normal of blood erythrocytes) were invariably from patients with non-glomerular haematuria.

In comparison with their own venous red cells, the mean urinary MCV was reduced in glomerular patients and increased in patients with non-glomerular haematuria (Table 2). In order to ensure that individual results were independent of the size of circulating red cells, a comparison was made in each patient (Fig. 2). Red cells in the urine of patients with glomerulonephritis were invariably smaller than the circulating red cells, whereas 18 of the 21 patients with non-glomerular lesions had larger cells in the urine than in the circulation.

In those samples re-analysed after being left overnight at room temperature, the mean MCV rose slightly and insignificantly in both patient groups (Table 3).

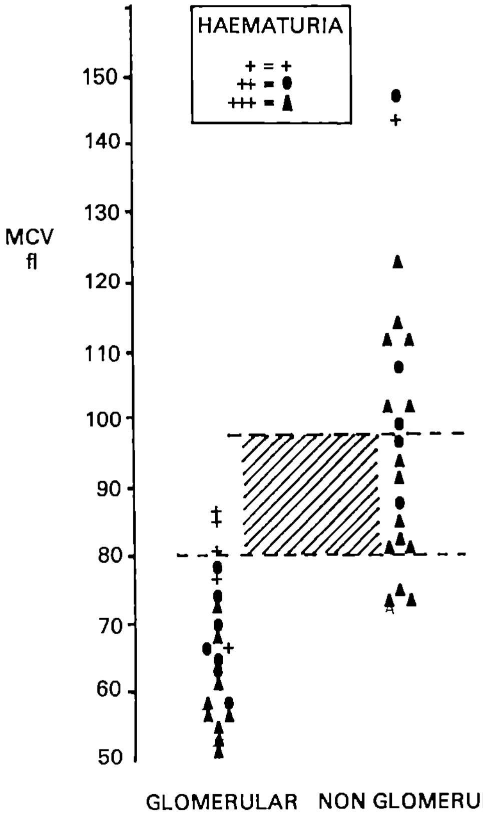

Fig. 1 Mean corpuscular volume of urinary erythrocytes $P<0.01$ between the 2 groups. Hatched area represents normal range of venous red cell MCV

Discussion

Occult haematuria is a common finding in health screening programmes, with a prevalence of 2 to 5% (Matti Vehaskari *et al.*, 1979; Ritchie *et al.*, 1986). Recent surveys have shown that full urological investigation results in a pathological diagnosis in up to 50% of cases (Carson *et al.*, 1979; Golin and Howard, 1979; Ritchie *et al.*, 1986). In the remaining patients, many will have a glomerulo-

Table 2 Comparison between the Mean MCV (fl) in the Urine and Blood

	Glomerular		*Non-glomerular*	
	Blood	*Urine*	*Blood*	*Urine*
Mean	88.9	68.5	88.9	99.4
SDM	3.7	10.2	5.1	20.4

$P<0.001$ in both groups

Table 3 Change in Urine MCV (fl) with Time

	Time	
	O	*Overnight*
Glomerular (n=9)	67.7±11.4	70.4±12.0
Non-glomerular (n=13)	100.8±18.9	101.5±16.7

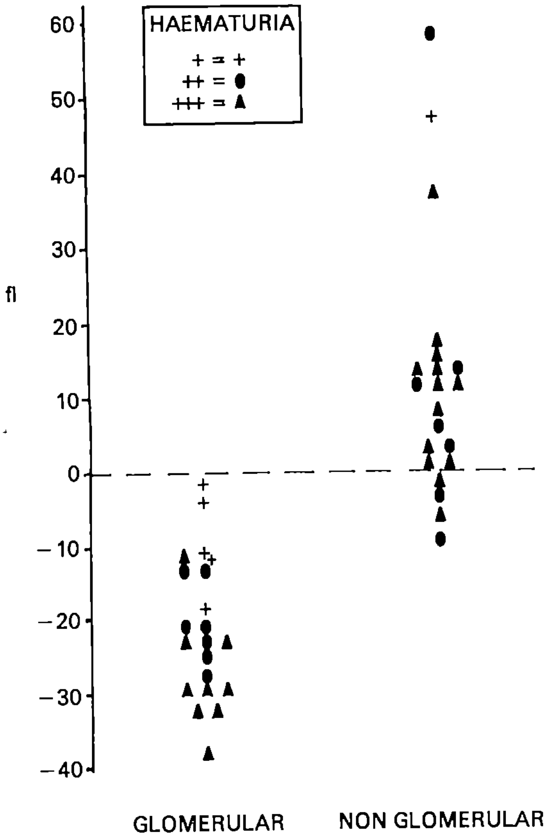

Fig. 2 Difference between mean corpuscular volume in urine and blood [i.e (MCV) urine—(MCV) blood] for each patient $P<0.01$ between the 2 groups.

nephritis even in the absence of urinary red cell casts (Fairley and Birch, 1982) or proteinuria (Kincaid-Smith and Dowling, 1980). A simple test to identify the source of bleeding in such patients would therefore have important clinical application and reduce unnecessary investigations.

It is disappointing that the microscopic appearance of red blood cells in the urine has not proved more reliable in differentiating between glomerular and non-glomerular bleeding. The variable results reported using phase contrast microscopy (Venkat Raman *et al.*, 1986) are probably due to the subjective nature of this technique. To overcome this problem the measurement of MCV of urinary erythrocytes by a Coulter Counter was first suggested in a brief report by Shichiri *et al.* (1986). The present work was designed to investigate this suggestion and to extend their observations.

We believe that our study justifies the following statements. The red cells in the urine of patients with biopsy-proven glomerulonephritis are generally smaller than those from patients with non-glomerular bleeding. As shown in Figure 1, however, there is some overlap between the 2 groups. Moreover, in order to use this finding prospectively, a source of reference must be given against which a urine sample from a patient with undiagnosed haematuria may be compared. One approach is to use the normal range of MCV of circulating venous red cells.

It can be seen in Figure 1 that of the patients with glomerulonephritis, 86% had MCVs below 80 fl, the lower limit of this range. Conversely, 86% of the patients with non-glomerular bleeding had MCVs >80 fl. However, all patients with urinary red cells in excess of the upper limit of normal for venous red cell size had non-glomerular blood loss. The reason why some of these cells were so macrocytic is not known. It is possibly related to the osmolality or sodium content of the urine samples and neither was measured in this study. This does not explain why abnormally large cells were never found in the urine of patients with glomerulonephritis unless the crenated erythrocytes are unable to swell under osmotic forces.

The size of red cells in the urine of an individual with haematuria will, of course, be affected by the size of those in their blood. In order to avoid this potential error, we compared the size of urinary cells in each urine sample with those in the blood of the same patient. With this modification (Fig. 2) our study demonstrates that for any patient, urine MCV less than that of their blood predicts a glomerulonephritis with a sensitivity of 100% and specificity of 84%. For those with urine MCV greater than blood MCV, a non-glomerular source is predicted with a sensitivity of 81% and a specificity of 100%.

Our study was restricted to patients with haematuria of at least 1+ on semi-quantitated stick testing. The urine of patients with less than this degree of haematuria tended to give irregular frequency histograms even when the sediment from several aliquots of centrifuged urine were analysed together. As can be seen from Figures 1 and 2, even with 1+ haematuria, results tended to be less discriminating than when heavier blood loss was present.

The time of voiding may not be critical for this analysis as the MCV of urinary erythrocytes changed very little when the samples were measured again after overnight storage at room temperature. It should be emphasised, however, that a comparison of the 2 groups was only performed on urine freshly voided, so the conclusions cannot necessarily be extended to samples analysed at other times.

In summary, Coulter analysis offers an objective method for predicting the source of haematuria. The test is simple and is performed in 10 min by a laboratory technician. Glomerulonephritis is strongly indicated by a urinary erythrocyte MCV of less than 80 fl or urinary red cells smaller than those in the patient's blood. A non-glomerular source is suggested by a urinary MCV greater than 80 fl or urinary red cells larger than those in the patient's blood and is identified with confidence by the finding of urinary red cells that exceed the upper limit of venous red cell size.

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Combination of Blood Group ABH Antigen Status and DNA Ploidy as Independent Prognostic Factor in Transitional Cell Carcinoma of the Urinary Bladder

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Summary—The prognostic value of DNA ploidy and blood group (ABH) antigen reactivity was studied in a consecutive retrospective study of 230 patients with primary transitional cell carcinoma of the urinary bladder. In 195 cases the DNA ploidy and ABH reactivity could be assessed in paraffin-embedded tissue. Early progression (in the first 3 years) occurred in 2% of the patients with diploid ABH positive tumours and in 31% of those with aneuploid ABH negative tumours. The 5-year survival rates corrected for intercurrent mortality were 95 and 56% respectively. In a Cox multivariate analysis, T category, age at diagnosis and histological grade emerged as significant independent prognostic indicators of bladder cancer death, whereas ABH reactivity and DNA ploidy had no significant independent value. However, if the combination of ABH reactivity and DNA ploidy was included in the Cox model, this and T category were independent predictors. When this Cox model was applied to assess the risk of progression, the only independent prognostic factor was the combination of ABH reactivity and DNA ploidy.

The histological grade and clinical stage (T category) are the criteria that have been mainly used for predicting the behaviour of a bladder tumour. Nevertheless, it is apparent that these are of limited value in assessing the prognosis. The inability to predict which patients with superficial bladder tumours will develop infiltrative cancer is one of the difficulties in the clinical management of patients with this disease. The mortality seems to be equally high among patients with secondary and those with primary muscle invasion (Kaye and Lange, 1982; Malmström *et al.*, 1987). It is therefore important to find tumour markers that can better identify high-risk tumours. Two promising markers of the invasive capacity are deletion of cell-surface blood group (ABH) isoantigens and tumour-cell aneuploidy. Earlier studies have indicated that these markers are, at least to some degree, independent, and furthermore that they are independent of the grade and stage of the disease (Borgström, 1987; Orihuela *et al.*, 1987).

The present study was part of an investigation of a retrospective consecutive bladder cancer study. Initially, attempts were made to standardise and refine available techniques for assessing ABH antigen expression and DNA ploidy in paraffin-embedded material (Busch *et al.*, 1988; Malmström, 1988). The prognostic implications of ABH expression (Malmström *et al.*, 1988) have been reported elsewhere.

The purpose of the present study was to evaluate (1) the correlation of tumour marker profile with histological grade and T category, (2) the prognostic value of DNA ploidy alone and (3) the prognostic value of DNA ploidy and ABH reactivity in combination regarding the primary bladder tumour.

Patients and Methods

All patients with newly detected transitional cell carcinoma of the urinary bladder seen at the University Hospital, Uppsala, between 1975 and 1978 were studied retrospectively. The total series

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comprised 230 patients aged 34 to 94 years (mean 68), with an observation time ranging from 5 to 9 years (mean 6.5). No patient was lost to follow-up. The clinical outcome in relation to grade, T category and treatment has been reported elsewhere (Malmström *et al.*, 1987).

The immunostaining method for the A, B and H isoantigen employed mouse monoclonal antibodies against A and B, and the *Ulex europeus* lectin for identification of H substance. A biotinylated rat monoclonal antibody against mouse immunoglobulin was used as the second layer and a commercial avidin-biotin-peroxidase complex as the third. The evaluation of results was based on both the extent and intensity of the staining. A semiquantitative scale was used, each tumour being given a score between 0 and 12. Tumours with scores of 4 or less represented no, or very weak, expression and were called ABH negative. Those with a score of more than 4 represented strong expression and were called ABH positive. Details of this method have been described previously (Busch *et al.*, 1988).

For determination of DNA ploidy, sections 100 µm thick were cut from paraffin-embedded blocks. The sections were immersed in xylol, rehydrated in alcohol and, finally, with distilled water. The tissue was homogenised and enzymatic dispersion and digestion were achieved with 0.2% protease (Sigma, St Louis, USA). The suspension was vortexed and tissue clumps removed by filtration. The single cell suspensions were centrifuged, the supernatant removed and the pellet resuspended in phosphate-buffered saline (PBS). The suspension was added to 400 µl Percoll solution (Pharmacia AB, Uppsala), 45% in PBS, and centrifuged. Three layers were formed: a supernatant, a thin nuclear band and the Percoll cushion. The fractions were separated and diluted, after which 15 µl propidium iodide were added. After 15 min the samples were ready for measurement. The thin band usually provided the best histogram. The cellular DNA content was measured using a Leitz MPV flow cytometer. Details regarding the method and correlation of DNA ploidy to grade and T category have been described by Malmström (1988).

All flow cytometry measurements and determinations of ABH reactivity were performed without knowledge of histological grade, T category or clinical outcome. The histological material was re-examined and graded according to a modification of the classification of Bergkvist (Malmström *et al.*, 1987) without the examiner having knowledge of either the former grading or the patient's history.

Analysis of the impact of ABH reactivity and DNA ploidy on the cancer mortality was based on all patients. It was our original aim that all patients with Ta-T1 tumours should be analysed concerning progression of the T category. However, at the time of the study radical treatment had often been instituted in patients with high grade T1 tumours, making the analysis of progression impossible in this subgroup. Thus the analysis comprised a selected group of Ta-T1 tumours, judged to be low risk tumours on the basis of grade and T category, that had mainly been treated by transurethral resection. Any of these patients who developed a tumour of higher T category during follow-up were designated progressors.

The survival and non-progression curves were calculated by the life-table method with the BMDP computer program (BMDP Statistical Software, Department of Biomathematics, University of California Press, Los Angeles, USA) and survival was corrected for intercurrent death. Multivariate analyses were performed with the proportional hazards method of Cox.

Results

In 195/230 primary tumours (85%), both markers could be determined; 48 tumours (25%) were diploid and ABH positive and 77 (39%) were aneuploid and ABH negative. A large proportion were diploid and ABH negative (60; 31%) and a small proportion were aneuploid and ABH positive (10; 5%) (Fig. 1). Thus the diploid tumours were almost equally ABH positive or negative, while the aneuploid tumours were usually ABH negative. Of the aneuploid ABH negative tumours, 0, 12, 48 and 76% were detected among tumours of grade 1, 2A, 2B and 3–4 respectively (Fig. 2). The corresponding

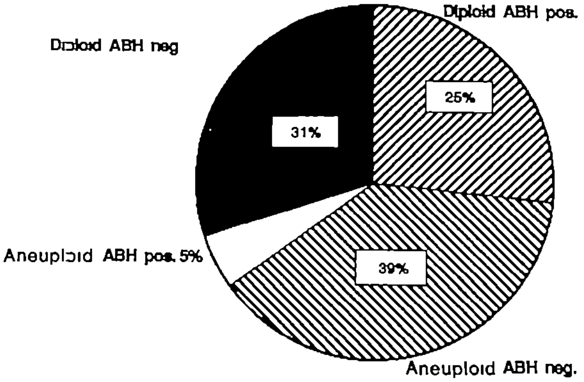

Fig. 1 Relationship of DNA value and ABH expression in 195 cases of transitional cell carcinoma

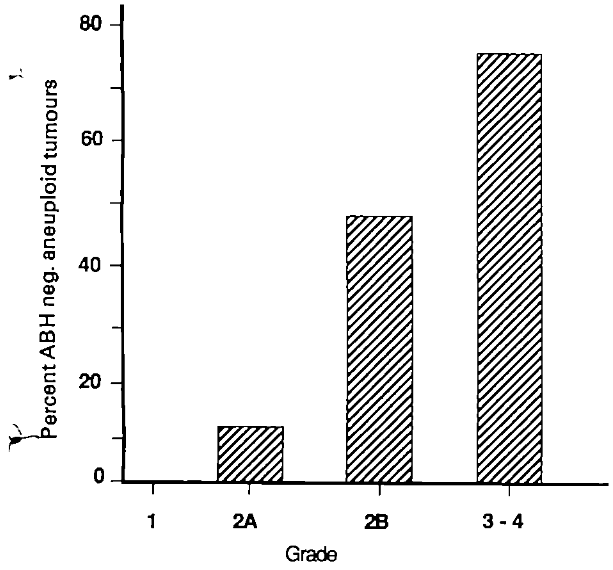

Fig. 2 Relationship of DNA value/ABH expression and histological grade. The percentage number of aneuploid ABH negative tumours in the different grades were · 0% in G1, 12% in G2A, 48% in G2B and 76% in G3–4.

figures for categories Ta, T1, T2, T3 and T4 were 15, 48, 64, 54 and 88% respectively (Fig. 3). The diploid ABH negative tumours were mainly low grade, but a relatively large number were found in patients with a high T category. The small group of aneuploid ABH positive tumours were all high grade (Tables 1 and 2).

There were 103 patients with superficial tumours that could be evaluated regarding progression; of these, 81 were diploid and 22 aneuploid. In an analysis of progression the aneuploid tumours were found to have progressed more often than the diploid ones. The difference was apparent mainly during the first 2 years and lasted during the whole follow-up ($P<0.002$) (Fig. 4). The cumulative proportions of non-progressing diploid and aneuploid tumours were 92 and 67% at 3 years, and 83 and 62%, respectively, at the end of follow-up (9 years). On correlation of DNA ploidy to corrected survival, a significant difference was found between the 108 diploid and the 87 aneuploid tumours ($P<0.0001$) (Fig. 5). The 5-year survival rates among patients with diploid and aneuploid tumours were 84 and 57% respectively. Patients with aneuploid tumours seem to have a worse prognosis even if they survived the first 5 years of follow-up.

On correlation of the 2 combined markers to progression, a significant difference was found between the patients with diploid ABH positive tumours (43) and those with aneuploid ABH negative tumours (20) ($P<0.008$) (Fig. 6). The cumulative proportions of non-progressing tumours in these 2 groups were 98 and 69% at 3 years, and

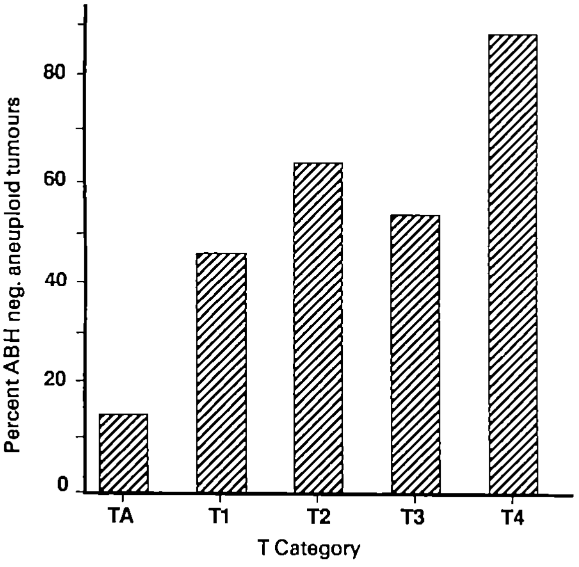

Fig. 3 Relationship of DNA value/ABH expression and T category. The percentage numbers of aneuploid ABH negative tumours in the different categories were · 15% in Ta, 48% in T1, 64% in T2, 54% in T3 and 88% in T4

Table 1 Combinations of DNA Ploidy and ABH Expression in Relation to Histological Grade

Histological grade	*Diploid ABH−*	*Diploid ABH+*	*Aneuploid ABH−*	*Aneuploid ABH+*	*Total*
G1	9	17	0	0	26
G2A	33	20	7	0	60
G2B	9	9	22	6	46
G3–4	9	2	48	4	63
Total	60	48	77	10	195

Table 2 Combinations of DNA Ploidy and ABH Expression in Relation to T Category

T category	*Diploid ABH−*	*Diploid ABH+*	*Aneuploid ABH−*	*Aneuploid ABH+*	*Total*
Ta	29	42	13	1	85
T1	14	5	20	3	42
T2	8	0	18	2	28
T3	8	1	14	3	26
T4	0	0	7	1	8
Total	59	48	72	10	189

Tis and Tx cases excluded

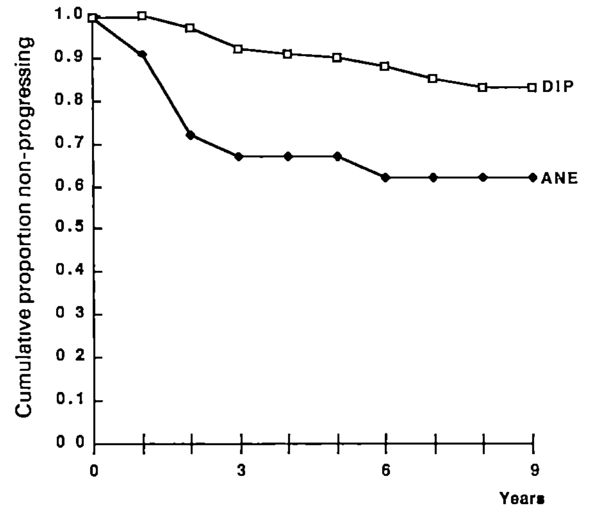

Fig. 4 Non-progression rates in relation to DNA ploidy among 81 patients with diploid (DIP) tumours and 22 with aneuploid (ANE) tumours ($P<0.002$)

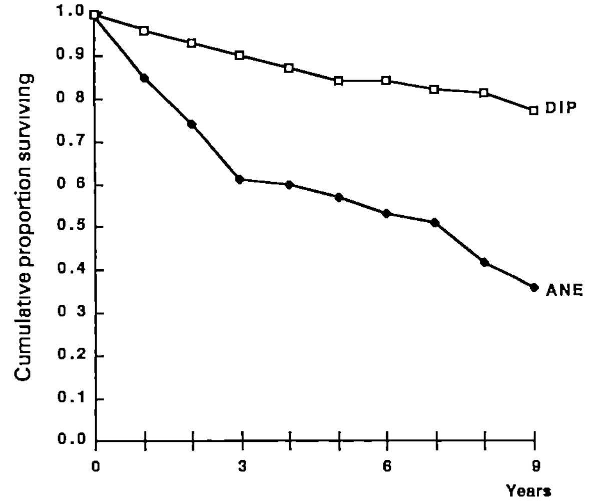

Fig. 5 Corrected survival rates in relation to DNA ploidy among 108 patients with diploid (DIP) tumours and 87 with aneuploid (ANE) tumours ($P<0.0001$)

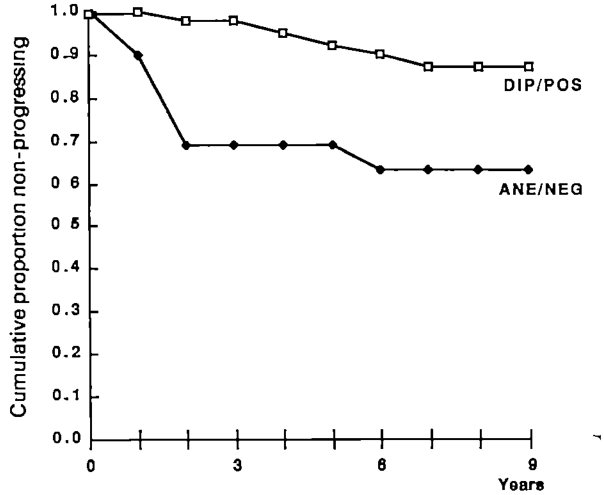

Fig. 6 Non-progression rates in relation to DNA ploidy and ABH expression among 43 patients with diploid ABH positive (DIP/POS) tumours and 20 with aneuploid ABH negative (ANE/NEG) tumours ($P<0.008$).

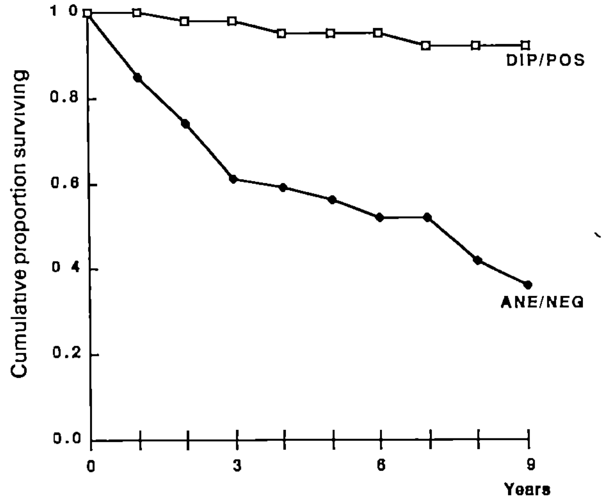

Fig. 7 Corrected survival rates in relation to DNA ploidy and ABH expression among 48 patients with diploid ABH positive (DIP/POS) tumours and 77 with aneuploid ABH negative (ANE/NEG) tumours ($P<0.0001$).

87 and 63% at 9 years, respectively. The corrected survival rate was significantly higher among the 48 patients with diploid ABH positive tumours than among the 77 patients with aneuploid ABH negative ones ($P<0.0001$) (Fig. 7). The rates at 5 years for these 2 groups were 95 and 56% respectively. The results for the 70 patients with discordant markers were intermediate. The corrected survival differed significantly both from that in the group with favourable markers and in the group with unfavourable markers ($P<0.05$) and the 5-year survival rate was 74%. As regards progression, among the patients with discordant markers (n = 40), 76% showed non-progression at 9 years. This rate was significantly higher than that found in patients with adverse markers ($P<0.02$) but did not differ from those with favourable markers. When this group of 40 patients was subdivided according to ploidy and ABH expression, patients with diploid ABH negative tumours showed a non-

Table 3 Cox Analysis for Corrected Survival in 195 Patients with Bladder Cancer

	Univariate statistics (unadjusted Chi-square)		*Multivariate statistics*			
			Model a		*Model b*	
Variable	*Chi-square*	*P*	*Chi-square*	*P*	*Chi-square*	*P*
Age	7.27	0.007	4.76	0.0291		N.S.
Sex	0.80	N.S.		N.S.		N.S.
T category	57.13	<0.0001	12.69	0.0004	26.60	<0.0001
Grade	34.27	<0.0001	9.46	0.0291		N.S.
DNA	19.70	<0.0001		N.S.		—
ABH	12.46	0.0004		N.S.		—
DNA and ABH	28.02	<0.0001	—	—	20.72	0.0011

a = with ABH and DNA separated b = with ABH and DNA combined.

progression rate of 78% at 9 years (n = 38) and a 5-year survival rate of 75% (n = 60). Among the patients with aneuploid ABH positive tumours, the non-progression rate at 9 years was 50% (n = 2) and the 5-year survival was 48% (n = 10). However, this group was very small.

In order to find out the relative importance and "independence" of ABH reactivity and DNA ploidy as prognostic factors in bladder carcinoma, 4 variables, namely patient's age at diagnosis, (70 years or 70 years and older), sex, histological grade and T category were compared with the tumour markers with respect to their association with corrected survival using Cox's proportional hazard model. When analysed separately, all variables except sex were found to be associated with corrected survival (Table 3). The relative risk (odds ratio) of death from bladder cancer within each variable was calculated as shown in Table 4. The marker combination was applied to all of the various marker profiles and also when the small group of aneuploid ABH positive cases were excluded because of their limited numbers. The first investigation yielded a significant difference between patients with a favourable marker profile and those with discordant markers. When the aneuploid ABH positive cases were excluded there was a significant difference between all 3 combinations. In the multivariate analysis age, grade and T category were independently associated with death from bladder cancer, whilst this was not the case with DNA ploidy or ABH reactivity. When the latter 2 markers were combined (DIP, ABH+ versus ANE, ABH+/DIP, ABH– versus ANE, ABH–) and included in the Cox model, only T category and the marker combination were independently associated with survival (Table 3). When the aneuploid ABH positive cases were excluded from the model, this did not alter the independency of the factors; neither did subdivision of the tumour grade into low grade (1–2A) and high grade

Table 4 Odds Ratios (O.R.) for the Risk of Death from Bladder Cancer (95% confidence intervals in parentheses)

Variable	*O.R.*	*P*
Age at diagnosis (years)		
<70	1.0	0.0075
≥70	1.88 (1.16–3.03)	
Sex		
Male/Female	N.S.	
T category (TA–T4)		
*T	1.0	<0.0001
T+1	1.45 (1.33–1.58)	
Grade (G1, G2, G2B, G3–4)		
†G	1.0	<0.0001
G+1	2.28 (1.71–2.95)	
ABH reactivity		
Positive	1.0	0.001
Negative	2.74 (1.44–5.21)	
DNA ploidy		
Diploid	1.0	<0.0001
Aneuploid	1.95 (1.46–2.61)	
DNA and ABH		
DIP/ABH+	1.0	0.0085
DIP/ABH–	4.52 (1.32–15.52)	
DIP/ABH–	1.0	0.0018
ANE/ABH–	2.45 (1.37–4.38)	

* T compared with T + 1 designates any one of the possible steps in the following scale: Ta-T1-T2-T3-T4.
† G compared with G + 1 in the scale: G1-G2A-G2B-G3–4.

(2B–3/4). In a multivariate analysis of progression, with the tumour markers included separately, DNA ploidy emerged as the only independent prognostic factor. When ABH reactivity and DNA ploidy were combined, this combination provided the only independent prognostic factor for progression.

Discussion

Several tumour marker systems have been used to classify histologically similar tumours into those with low and high potential for deep invasion. There are indications that the use of a combination of multiple markers is more effective than a single marker (Weinstein *et al.*, 1984; Orihuela *et al.*, 1987).

There has been some controversy as to the clinical value of ABH reactivity in bladder carcinoma. Zingg and Wallace (1985) regarded it as a test that gave additional prognostic information. Lange and Whinfield (1987) were of the opinion that ABH isoantigen deletion appeared to correlate with invasiveness but that the methodology had not yet been standardised to the extent required for its introduction into routine pathology. Our initial objective was to improve the methodology (Busch *et al.*, 1988). The subsequent analysis of ABH reactivity *per se* indicated that it is of prognostic value but that sensitivity and specificity are too low for it to be adopted as a predictive test in isolation (Malmström *et al.*, 1988).

Modal DNA values have been reported to correlate well with grade, T category, recurrence rate, risk of progression and death from cancer (Hofstaedter *et al.*, 1984; Gustafson and Tribukait, 1985; Tribukait, 1987). Paraffin-embedded material has been found to be reliable for such analyses in several studies (Hedley *et al.*, 1983; Fosså *et al.*, 1986). In the present study only paraffin-embedded material could be obtained, and the results agree with the findings of those authors who found DNA measurements to be of prognostic value.

The report by Anderström *et al.* (1980) on the prognostic importance of lamina propria invasion in superficial bladder tumours has gained wide acceptance (Stöckle *et al.*, 1987). The present study supports this conclusion, as category T1 tumours resemble muscle invasive tumours with regard to their tumour marker profile. It seems that DNA ploidy shows more correlation to histological grade than ABH expression. DNA determination can be used to improve reproducibility and may replace grading in future.

Other observations indicate that ABH deletion occurs at an earlier stage of tumour development than aneuploid DNA modal values (Borgström, 1987). This agrees with our finding that 70% of the tumours were ABH deleted while only 44% were aneuploid.

It must be emphasised that the marker profile can change during the clinical course of the disease. Sequential determination of these markers in bladder washings has been claimed to be valuable both in predicting the course of a patient's disease and in monitoring the response to intravesical BCG (Orihuela *et al.*, 1987).

In the present investigation, ABH reactivity was found to be useful for predicting early progression, but this prognostic value disappeared during long-term follow-up (Malmström *et al.*, 1988). By contrast, DNA ploidy emerged as predictive even in the long term. In 1 series, 16% of aneuploid tumours changed after resection to diploid tumours on recurrence, while 21% of the initially diploid tumours changed on recurrence to aneuploid during the 2.6-year observation period (Tribukait, 1987). Follow-up assessment of ABH isoantigen expression is reported not to provide any further prognostic information (Borgström, 1987). The difference in prognosis between patients with a favourable and those with an unfavourable marker profile seems to become manifest during the first 2 years of follow-up. This is an indication of the short time available for treatment if the clinical course of the disease is to be changed.

We are currently investigating the value of these markers in a prospective series using fresh tissue, which may prove more reliable. The existence of aggressive tumours that are ABH positive and diploid is a reality. There are many complexities regarding ABH isoantigen expression (Busch *et al.*, 1988) and some tumours have DNA derangements detectable only by karyotyping, and without being frankly aneuploid. These facts require further investigation.

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Long-term Clinical Results using the Artificial Urinary Sphincter around Bowel

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Summary—Four patients are presented in whom bowel was used to reconstruct a bladder. As a sphincteric mechanism was absent in all 4, the cuff from the artificial urinary sphincter was placed around the bowel to provide continence. This allowed for "normal" urination. The longest follow-up period was 11 years and the shortest 1.5 years. Both clinical and experimental data show that bowel will tolerate compression from the artificial urinary sphincter provided infection does not supervene and the pressure does not exceed 80 cm of water.

Current interest in total bladder replacement with bowel is reflected in the great number of articles now appearing in the literature. Management of the urinary stream following radical cystectomy includes construction of a low pressure reservoir from bowel using a variety of techniques. Indeed, this procedure has become the "Origami" of urological operations. Continuity of the urinary tract has been maintained by anastomosis of the reservoir to the urethra, as in the Camey procedure or Le Bag (Camey, 1985; Light and Engelmann, 1986). Continence depends on the residual distal urethral sphincteric mechanism. However, this procedure is possible only in males as radical cystectomy in females routinely includes the entire urethra and thus the sphincter. An alternative to a continent diversion in females would be the use of the artificial urinary sphincter as a continence mechanism around bowel which has been used to replace the bladder and urethra. The long-term clinical results in 4 patients who underwent this procedure form the basis of this report; 3 patients have previously been reported (Light and Scott, 1984).

Case Reports

The 4 cases are presented in detail as the clinical results closely mimicked the animal model experiments. The author was involved with the reconstructive aspect of the patients' treatment but not with the initial procedures.

Case 1. S.F., a female born with classical bladder exstrophy, underwent ureterosigmoidostomy for incontinence. Because of persistent anal incompetence and faecal soilage, she underwent bladder replacement with a tubularised segment of sigmoid colon at age 8 years (Light and Scott, 1984). The ureters were reimplanted into the proximal sigmoid bladder and the distal end anastomosed to the vaginal vestibule as a "urethra." The AMS742 artificial sphincter was implanted in 1977 with the cuff being placed around the distal portion of the sigmoid bladder. Although the surgery was technically successful, the patient experiences unpredictable urinary incontinence. At that stage, the importance of detubularising the bowel was not appreciated. In an attempt to gain continence, several revisions were performed over a 5-year period to increase progresssively the balloon pressure from the original 61 to 70 cm of water to 81 to 90 cm of water, simultaneously decreasing the cuff size. Cuff erosion did not occur until the 81 to 90 cm water balloon was inserted, necessitating removal of the device. The AMS 800 artificial urinary sphincter with a 71 to 80 cm water balloon and a 7 cm cuff was reimplanted 9 months later, in 1983. Continence was achieved only when a patch enteroplasty, to ablate the bowel contractions, was performed in 1984, together with the insertion of a smaller cuff. The patient has not required further surgery and is currently continent and voiding *per "urethram"* with normal upper tracts and serum biochemistry (Fig 1)

This patient illustrates that the large bowel is

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capable of withstanding pressures of up to 71 to 80 cm of water for many years. Apart from the short period of 9 months when the device was removed, the artificial sphincter has been functioning around bowel for 11 years.

Case 2. M.D., a female, was treated at age 2 years for sarcoma botryoides with chemotherapy, radiotherapy and radical hysterectomy. This resulted in a scarred, non-functional bladder and urethra, complicated by bilateral hydroureteronephrosis and urinary incontinence. She underwent bladder replacement with an isolated tubularised sigmoid loop in 1981 at age 7 years similar to S.F. (Light and Scott, 1984). The AMS792 was implanted 6 months later, in January 1982, using a 51 to 60 cm balloon and a 5.5 cm cuff. Again, unpredictable urinary incontinence occurred until a patch enteroplasty was performed in 1983 (Light, 1985). Revision for a cuff leak was performed in 1987 when the system was exchanged for the AMS800 model with the silicone-coated cuff.

The patient has been totally continent since 1983 with stable upper tracts and voids *per "urethram"* (Fig. 2). The urine has remained sterile. The sigmoid colon has been subjected to the cuff pressure continuously for 6.5 years.

Case 3. L.T., a female born with meningomyelocele and a single left kidney, underwent a sigmoid conduit and subsequent cystectomy. She underwent urinary undiversion in 1984 at age 12 years using the Le Bag technique. The AMS800 was implanted simultaneously using a 6 cm cuff around the colonic portion of the bowel and a 61 to 70 cm balloon. The patient is continent with normal upper tracts and sterile urine, and voids using the Credé manoeuvre. She has been followed up for 3.5 years.

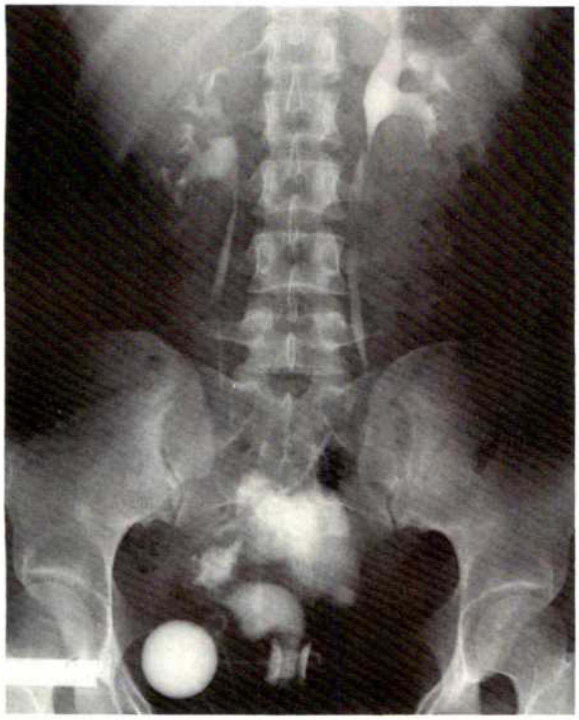

Fig. 1 IVU in Case 1 showing normal upper tracts 10 years after the original reconstruction.

Case 4. D.H., a male, was born with bladder exstrophy. He underwent ileal loop diversion at age 2 years followed by a cystectomy at age 12 years. The urethra was severed at the level of the urogenital diaphragm. Urinary undiversion was performed in January 1983 using a tubularised ileocaecal segment. The large bowel portion was anastomosed to the urethra and the ureters inserted into the ileum (Light, 1985). Simultaneous insertion of the AMS792 was performed using a 7.5 cm cuff and a 61 to 70 cm balloon. A smaller cuff was inserted 3 months later. Again, total continence was not achieved because of contractions from the tubularised bowel. Revision was required 18 months after the original insertion because of a loose connector. The device became infected, resulting in cuff erosion and removal of the device.

The AMS800 was reimplanted 2 years later but also became infected and the patient subsequently was converted to a continent diversion using the original ileocaecal segment.

This patient illustrates the devastating effect that infection plays in causing a cuff erosion. No erosion occurred during the 18 months prior to the development of infection, which followed a surgical revision. Cuff erosion occurred within 1 month from clinical evidence of an infected device.

Technique of Cuff Implantation

The technique of cuff implantation around bowel differs from that round the bladder neck or urethra. The technique currently used by the author has developed from previous experience with the cases described.

The cuff should be placed at the junction between the colonic tail and bowel reservoir. This will prevent peristalsis from the tubularised colonic portion forcing urine past the cuff. Mucous discharge from the portion of the bowel distal to the cuff site has not been profuse and none of the 3 female patients have complained of "vaginal" discharge. The cuff should pass through a 2-cm defect in the adjacent mesentery to maintain the cuff position until a sheath has formed. No incidences of cuff displacement or angulation occurred using this technique.

Cuff sizing is important and it is essential to have access to the lumen of the reservoir during this manoeuvre. The cuff sizer, or umbilical tape, is passed around the bowel and gradually tightened

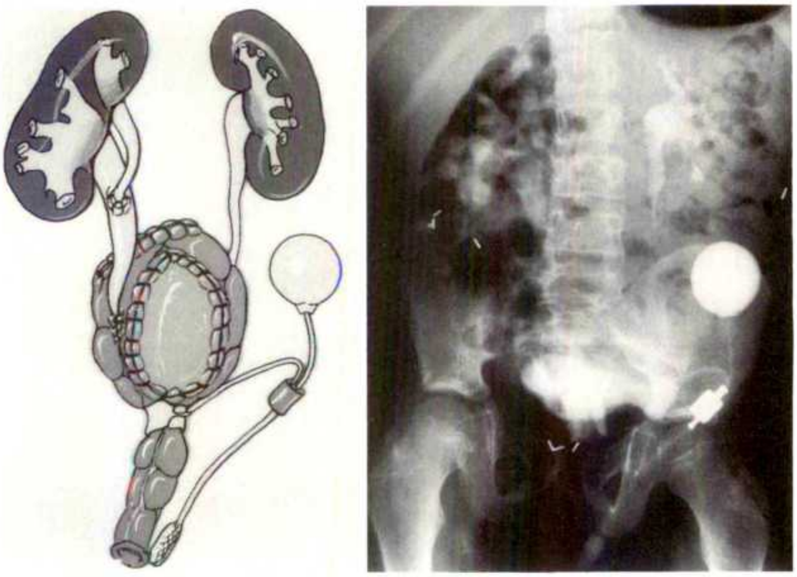

Fig. 2 IVU in Case 2 illustrating the patch enteroplasty associated with normal upper tracts 6 years after the original reconstruction.

until the tip of the fifth finger placed from inside the bowel lumen passes snugly through the sizer. Crenation of the bowel wall usually occurs to some degree during this manoeuvre. The cuff size was previously determined by loosely fitting the sizer without causing any crenation. This, however, necessitated replacement with a smaller cuff soon after surgery owing to crenation of the bowel wall from compression. This resulted in the cuff becoming too large and therefore relatively inefficient.

The cuff size appropriate for use around the large bowel in this series was 5.5 or 6.0 cm in length. A fibrous sheath is formed beneath the cuff maintaining the bowel wall in the folded or crenated position. This has not resulted in interference with cuff closure or opening in the clinical situation. The tubing from the cuff should lie anterior to the bowel reservoir to facilitate re-exploration.

In the presence of a highly compliant, low pressure reservoir such as Le Bag, the 51 to 60 cm or 61 to 70 cm balloon is recommended. This is lower than the balloon pressure generally used around the bladder neck as the bowel wall is more compliant than the detrusor muscle and so requires less pressure to obtain a watertight seal.

Discussion

It is now technically possible to create a low pressure urinary reservoir using a segment of bowel. Restoration of urinary tract continuity with this type of reservoir following radical cystectomy has been limited to those male patients with a functioning distal urethral sphincter. In the event that this failed and urinary incontinence resulted, the artificial urinary sphincter has been inserted to obtain continence, with the cuff being placed around the bulbar urethra.

Construction of a continent urinary diversion has been the only alternative in females, or even in males with absence of the distal sphincter mechanism. The long-term follow-up of the patients in this report indicates that replacement of the urethra and bladder with bowel in females, together with the artificial sphincter around the bowel, is a viable alternative. Early experience with tubularised bowel segments and initial incontinence in 3 of the 4 patients reported above clearly indicates the necessity to disrupt the directional peristalsis in order to create a low pressure reservoir (Light, 1985). This is critical when considering placing the cuff around a bowel segment. The high pressures generated by the tubularised bowel contractions are capable of overcoming the cuff pressure, resulting in urinary incontinence. The construction of a low pressure reservoir allows a lower pressure balloon to be used, thus significantly decreasing the chances of pressure necrosis with cuff erosion. Experience gained with these 4 patients has led to the technique of cuff measurement described above.

Animal studies were performed at this institution to evaluate the effects of cuff pressure on the bowel (Engelmann *et al.*, 1985; Engelmann *et al.*, 1985). The cuff was placed around isolated segments of either the appendix or caecum in rabbits. The isolated bowel segment, cuff and balloon, were intraperitoneal, while the pump was placed subcutaneously. The balloon pressures ranged from 40 to 100 cm of water. Necropsy examination revealed findings analogous to those in the human in that a fine capsule developed around the cuff and around the bowel beneath the cuff. The latter did reduce the luminal size in the animal. The free-floating reservoir showed no fibrous capsule in the absence of infection.

Similar findings were present in the human subjects during surgical revision. In particular, the fibrous capsule beneath the cuff similarly reduced the lumen as it has been formed with the bowel in the crenated position. This narrowing of the bowel lumen, however, has not resulted in any clinical voiding problems on long-term follow-up.

Pressure necrosis of the bowel wall in the rabbit occurred only with pressures in excess of 80 cm of water and in the absence of infection. If infection was present, erosion occurred at much lower pressures. Identical findings occurred in Case 1, where erosion occurred soon after implanting the 81 to 90 cm balloon, even though several balloons of lower pressure had been present for 5 years.

Further experiments in dogs were performed at this institution and involved placing the cuff around a small bowel segment. These yielded similar results when related to the sheath around the cuff and the absence of intra-abdominal adhesions (Engelmann *et al.*, 1985). The canine ileum, however, could withstand pressures of 70 to 86 cm of water without erosion occurring, contrary to the situation found in rabbits where pressures in excess of 80 cm of water resulted in bowel necrosis. Thus both the large and small bowel in the animal models could tolerate pressures of up to 80 cm of water without pressure necrosis occurring. It should be emphasised that the cuff had only been implanted around a large bowel segment in humans. The feasibility of using small bowel in humans is unknown, although the canine model does support this possibility.

The only significant difference between the animal model and human subjects was the development of bowel adhesions in the latter. This was present in all subjects undergoing surgical revision and was unrelated to the presence of an infected device. As the balloon had deliberately been placed directly up against the anterior abdominal wall (intraperiotoneally), the bowel adhesions did not involve this component. They resulted in intestinal obstruction in 1 patient but this responded to conservative treatment.

Microangiography and histology of the animal cuff site yielded important data (Engelmann *et al.*, 1986). The mucosa generally showed atrophy but the muscularis remained intact with no loss of vascularity or cell mass. Indeed, new vessel ingrowth associated with the fibrous sheath formation was noted.

The long-term clinical results indicate that the bowel can sustain the prolonged pressure exerted by the cuff, provided the balloon pressure does not exceed 80 cm of water. Currently it is recommended that the 61 to 70 cm or 51 to 60 cm balloon be used as higher pressures are unnecessary to obtain a watertight seal. However, a low pressure bowel reservoir is essential. Using these principles, 3 of the 4 patients obtained urinary continence with the ability to urinate *per "urethram"*.

The mechanical reliability of the artificial sphincter is important when considering major reconstructive surgery. Since the introduction of the silicone-coated cuff in May 1983, this reliability has improved significantly. To date, the author has inserted this type of cuff in 84 patients, with a varied aetiology for their incontinence. The mean follow-up period is 38.4 months (range 4–60), during which time no mechanical failure of the device occurred.

Because of the improved techniques currently available to create a low pressure reservoir from bowel and the satisfactory experimental and clinical results with the artificial sphincter around bowel, this method offers a technique of total reconstruction of the lower urinary tract. Female patients with benign or malignant vesical problems requiring cystectomy could benefit from this and thus avoid a stoma. As with other reconstructive procedures, however, careful patient selection is required to ensure success.

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Study of Appropriate Antibiotic Therapy in Transurethral Prostatectomy

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Summary—Septicaemia is the commonest cause of morbidity and mortality following transurethral prostatectomy. Routine blind antibiotic prophylaxis is not always effective and there is a tendency to over-use potent new and expensive antimicrobials. Attempts to "sterilise" the urine pre-operatively are also expensive and disruptive. However, appropriate treatment/prophylaxis can be administered economically using rapidly obtained laboratory results. We describe here a technique of routine direct antibiotic sensitivity testing (DST) of the patient's urine pre-operatively and before catheter removal. Such testing can be performed by junior medical staff in a ward side-room. An appropriate antibiotic may then be administered parenterally 1 h before surgery or catheter removal.

A total of 102 consecutive patients underwent TURP and only 1 of those with infected urine became septicaemic. In this instance, an appropriate antibiotic had been incorrectly given orally before removal of the catheter.

If the antibiotic sensitivities of a patient's urine are known, and an appropriate antibiotic is given parenterally 1 h pre-operatively or before catheter removal, the incidence of septicaemia following transurethral surgery may be significantly reduced.

Symptomatic benign prostatic hyperplasia will develop in 10% of all men reaching the age of 40 (Lytton *et al.*, 1968). Transurethral prostatectomy (TURP) is a safe and effective treatment with an operative mortality of less than 1% (Mackenzies, 1973). However, bacteraemia was found in more than half of the men with infected urine during prostatectomy and other lower urinary tract surgery (Keighley and Burdon, 1979). This peri-operative bacteraemia is usually transient and symptomless, but in a few cases it may progress to septicaemia defined as protracted bacteraemia with fevers, chills and shock (Keighley and Burdon, 1979).

In this unit, post-operative septicaemia was the commonest cause of death following transurethral prostatectomy (Murphy *et al.*, 1983); 6 (0.34%) of 1604 men undergoing TURP during a 3-year period suffered a post-operative death and 4 of these men died as a result of septicaemia. Of the 18 patients who became septicaemic, 11 did so immediately after operation and 7 following catheter removal.

Bacteraemia also develops, though less frequently, during operations on patients with sterile urine (Sullivan *et al.*, 1973) but this rarely, if ever, leads to post-operative septicaemia (Cafferkey *et al.*, 1982).

In our experience, 30% of patients come to operation with urine already infected, usually resulting from indwelling catheters or from previous operations. The infecting bacteria are often mixed because many patients have already received antibiotics and many organisms are resistant to the commonly used antibiotics (Cafferkey *et al.*, 1980).

Specific chemotherapy of pre-operative bacteruria, due to organisms whose identity and antibiotic sensitivity is established, should drastically reduce the incidence of septicaemia. However, because patients are often admitted only a day or two before operation, adherence to standard techniques of urinary culture and sensitivity testing would disrupt

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operating lists and prolong the admissions of some patients.

To overcome this problem, a system of urine culture and direct sensitivity testing, both pre-operatively and before catheter removal, was introduced in 1980. This allows an appropriate antibiotic to be administered parenterally 1 h before these potentially hazardous events. Such antibiotics are not expected to sterilise the urine or to prevent bacteraemia, but by ensuring an adequate antibacterial concentration in the blood, septicaemia may be prevented. Recently, the antibiotic has been continued post-operatively until the catheter has been removed or subsequent urine culture and DST demonstrates infection with a different organism.

Direct sensitivity testing has been employed since 1980 for over 4000 transurethral prostatectomies. Before 1980, septicaemia occurred at the rate of 1/month in these patients (Cafferkey *et al.*, 1980). Since then the rate has fallen to approximately 1/year and investigation of each incident revealed a failure to follow the DST system (Cafferkey *et al.*, 1982). It was considered timely to reassess prospectively its value in a sample group of patients due to undergo TURP.

Patients and Methods

A group of 102 consecutive patients undergoing TURP was studied without the knowledge of the primary care doctors. Bacterial culture of the urine and direct sensitivity testing were performed 24 h pre-operatively, in the immediate post-operative period (if clinically indicated) and 24 h before removal of the catheter.

The patients' urine was cultured in a side-room laboratory in the urology department. Direct sensitivity testing was performed by inoculating diagnostic sensitivity test agar (Oxoid Ltd, Basingstoke) with a sterile cotton bud dipped in well mixed urine. This gave a suitable inoculum density on the plate for sensitivity testing if a significant infection was present (10^5 organisms/ml). A multidisk (Mast Laboratories, Liverpool) was placed on the surface of the plate. Eight antibiotics were incorporated (disc concentration μg); ampicillin (100), gentamicin (10), nitrofurantoin (200), sulphafurazole (100), trimethoprim (1.25), cefuroxime (30), amikacin (30) and cephradine (30). Plates were incubated at 37°C and although results could often be interpreted as early as 5 h incubation for 10 h was considered optimal. Most tests were performed by laboratory staff, but during the evening and at week-ends they were performed by appropriately trained surgical interns.

Early the following morning the DST result was read by the surgical intern. If indicated by a significant growth of bacterial colonies, an appropriate antibiotic was prescribed and the planned procedure (TURP or catheter removal) undertaken. The results and their interpretation were checked subsequently by a microbiology technician. This was performed in a side room laboratory by a technician in those instances where it was possible to identify the organisms either by appearance or by a "three-sugar screen". More difficult organisms requiring greater antibiotic sensitivities were sent to the main laboratory for full identification.

Results

Of the 102 men studied, 73 had no urethral catheter pre-operatively (group A), 21 were catheterised on admission (group B) and 8 had a urethral catheter *in situ* prior to admission (group C). Only 11 (15%) of those in group A had a pre-operative UTI (Table 1). In contrast, more than half of those in groups B and C had infected urine pre-operatively. Table 2 lists the organisms cultured (and their antibiotic sensitivities) from pre-operative urinary examination.

In 70 men the resection was completed in less than 60 min, in 20 it took longer than this, and in 12 cases this fact was not clearly recorded.

Two men in group A, with sterile urine pre-operatively, developed a UTI in the immediate post-operative period (Table 3). Another man in group B, whose urine had been previously sterile but who required a catheter change 2 h post-operatively, developed septicaemia 24 h later. *Proteus mirabilis* was cultured from both his blood and urine. In each of these men the resection had taken longer than 60 min.

Six men (3 from each of groups A and B) had infected urine just before catheter removal. The 3 men in group A had previously had sterile urine; 2 of these had appropriate parenteral antibiotic therapy and the catheter was removed uneventfully. The third man developed septicaemia within 24 h due to *Staphyloccus albus*. An appropriate antibiotic, cephradine, had incorrectly been given orally just prior to catheter removal, because of a urinary growth of the same organism.

Two of those in group B had sterile urine pre-operatively. The third man, already on ampicillin for a chest infection, had a UTI due to *Klebsiella*, (resistant to ampicillin), but no alteration in his

Table 1 Infective Complications

	Group A		*Group B*		*Group C*	
	Infected	*Sterile*	*Infected*	*Sterile*	*Infected*	*Sterile*
Pre-operative urine	11	62	8	13	5	3
Post-operative UTI	0	2	0	0	0	0
Post-operative septicaemia	0	0	0	1	0	0
UTI before catheter removal	0	3	1	2	0	0
Septicaemia after catheter removal	0	1	0	0	0	0

Table 2 Organisms and Antibiotic Sensitivities from Infected Pre-operative Urine

Patient no	*Organisms*	*Ampicillin/ Amoxacillin*	*Gentamicin*	*Nitrofurantoin*	*Sulphafurazole*	*Trimethoprim*	*Cefuroxime*	*Amikacin*	*Cephradine*
Group A									
8	*Staph. aureus*	R	R	S	R	R	S	S	R
36	*E. coli*	R	S	S	S	S	S	S	S
61	*E. coli*	S	S	S	S	S	S	S	S
65	*Streptococcus* spp	S	R	S	R	S	S	R	R
66	*E coli*	R	S	S	R	R	S	S	S
82	Diphtheroids ent								
85	*Klebsiella* spp	R	S	S	S	S	S	S	S
	Proteus	R	S	R	R	R	S	S	S
	Strep. spp.	S	R	S	R	S	S	R	R
86	*E. coli*	R	S	S	R	S	S	S	S
92	*E. coli*	S	S	S	S	S	S	S	S
94	*E coli*	R	S	S	R	R	N/D	N/D	N/D
	Proteus	S	S	R	S	R	N/D	N/D	N/D
100	*Ps aeruginosa*	R	S	R	R	R	R	S	R
Group B									
16	*Klebsiella* spp	R	R	S	R	R	R	S	R
17	*Streptococcus*	S	R	S	R	S	S	R	S
21	*E. coli*	R	S	S	R	S	S	S	S
28	*Staph albus*	S	S	S	S	S	S	S	S
38a	*Klebsiella* spp	R	R	R	R	R	S	S	S
58	*E. coli*	R	R	S	R	R	S	S	S
76	*Ps aeruginosa*	R	S	R	R	R	R	S	R
79	*Klebsiella* spp	R	N/D	S	S	S	S	N/D	N/D
Group C									
6	*Serratia liquefaciens*	S	S	S	S	S	R	S	R
72	*Serratia marcescens*	R	R	S	R	R	S	R	R
78	*E coli*	R	R	S	R	R	R	S	R
89	*E. coli*	R	S	S	R	S	S	N/D	N/D
99	*E coli*	S	S	S	S	S	S	S	S

N/D = Not Documented

Table 3 Infections in the Immediate Post-operative Period

Patient no	*Group*	*Pre-operative UTI*	*Post-operative infection*	*Organism*
42	A	No	UTI	*Staph. aureus*
74	A	No	UTI	*Escherichia coli*
69	B	No	Septicaemia	*Proteus mirabilis*

therapy was considered necessary. Prior to catheter removal he had a UTI due to *Enterobacter cloacae*. Following appropriate antibiotic prophylaxis the catheters were successfully removed in each of these 3 men.

Discussion

Recent reports have suggested that the use of antibiotics in conjunction with transurethral prostatic resection should be individualised (Haverkorn, 1984). This is supported by evidence that the use of routine antibiotic prophylaxis is ineffective (Ramsey and Sheth, 1983; Ferrie and Scott, 1984) and, as we and others have found, that many organisms are resistant to the commonly used agents (Cafferkey *et al.*, 1982). Therefore, no single predetermined antibiotic is totally reliable and prophylaxis can be effective only if appropriate antibiotics are selected by rapid pre-operative urine culture.

We believe our method of urine culture and direct sensitivity testing meets this requirement and provides a simple, safe and effective control of infective complications of transurethral surgery. Our method is also inexpensive (approximately £0.60/test), enabling us to use less costly and well established drugs.

Recently it has been our practice to continue the appropriate antibiotic (preferably taken orally) during the post-operative period. This may be unnecessary, as a single parenteral pre-operative dose may prevent septicaemia in the period between surgery and catheter removal. This will be assessed in a future study.

Bacteraemia is rare during operations on patients with sterile urine (Sullivan *et al.*, 1973). When it does occur, septicaemia is extremely unlikely (Cafferkey *et al.*, 1980, 1982) and so routine prophylaxis is generally considered inappropriate. However, this study suggests that blind antibiotic prophylaxis should be considered following a lengthy resection or when there has been a break in the closed system of catheter drainage for clot evacuation or change of catheter.

Urine is probably the main source of pathogens entering the circulation at the time of transurethral surgery as evidenced by the presence of the same organism in urine and blood in the majority of cases (Morris *et al.*, 1976; Grabe, 1987). Other sources, for example the urethral flora and intraprostatic pathogens, must be considered responsible for bacteraemia in those patients with sterile urine. Robinson *et al.* (1982) found that 70% of patients had positive cultures from prostatic tissue and concluded that this was the most important factor associated with bacteraemia.

The association between duration of resection and peri-operative infective complications is interesting. A lengthy resection provides an opportunity for exogenous infection and usually indicates the presence of a large gland, possibly harbouring a large bacterial load. There is probably a case for selective antibiotic prophylaxis in cases where the resection time approaches 60 min.

Catheter removal following transurethral surgery is a recognised factor in severe infectious complications. The single patient in our study who became septicaemic following catheter removal was given oral cephradine 1 h previously because of *Staph. albus* urinary infection. This organism was sensitive to this agent but it is likely that, following oral administration, inadequate circulating levels were present at catheter removal. On development of the septicaemia, cloxacillin was added to therapy and continued for 5 days. The *Staph. albus* urinary infection was again noted 6 weeks following discharge from hospital.

The risk factors for infective complications associated with TURP demand prompt attention. Pre-existing urinary infection is undoubtedly of vital significance and our method of choosing appropriate antibiotic therapy is a practical demonstration of the efficient use of peri-operative antibiotics.

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Management of Localised Prostatic Carcinoma

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Summary—Localised carcinoma of the prostate may be amenable to radical curative therapy. Staging pelvic lymphadenectomy is controversial but is the only means of demonstrating lymph node spread accurately. Five patients in a group of 16 who presented apparently with localised prostatic carcinoma, and who had negative bone scan and CT scan, were shown at operation to have metastatic carcinoma involving their lymph nodes; 3 of 8 patients with high grade tumours were free of lymph node metastases. Without staging lymphadenectomy, these patients may have been inappropriately treated.

Carcinoma of the prostate is the fourth most common malignancy in the United Kingdom, 6000 new cases presenting each year. In the past, management has been directed towards surgical relief of mechanical outflow obstruction with the subsequent instigation of various forms of hormonal therapy in the hope of either retarding the development or relieving the symptoms of established metastatic disease. There has been increasing interest recently in possibly curative management in patients presenting with early or locally confined disease. There is, however, considerable controversy as to whether radical radiation therapy or radical surgery offers the best prospect of "progression-free" survival (Paulson *et al.*, 1982). It may be that, in the past, inaccurate staging of disease at presentation and failure to consider the grade of tumour have led to comparison of dissimilar groups, thereby invalidating any conclusions drawn about treatment regimens.

In most series, staging of prostatic carcinoma is by clinical examination, bone scan and either lymphangiography or CT scanning. Localised and presumptively curable disease would be confined to the prostate with no evidence of extracapsular spread, regional node involvement or detectable bony metastases.

The place of staging pelvic lymphadenectomy is still a matter of debate, yet few people would consider any form of radical local therapy in the presence of demonstrable regional node metastases. That regional lymph node involvement cannot be accurately demonstrated by lymphangiography has been shown by O'Donoghue *et al.* (1976), Paulson *et al.* (1979) and Grossman *et al.* (1980), who reported false negative rates ranging between 22 and 36%, observing that the obturator nodes were the most common source of error. CT scanning, whilst being a sensitive indicator of pelvic lymph node enlargement, cannot distinguish the presence of metastatic adenocarcinoma in normal-sized nodes (Golimbu *et al.*, 1981). Several authors (Wilson *et al.*, 1977; Brendler *et al.*, 1980; Grossman *et al.*, 1980) have noted the association of increasing tumour grade in prostatic tissue and the presence of lymph node involvement proven histologically at lymphadenectomy; Kramer *et al.* (1980) predicted that those with a Gleason score between 2 and 4 would be node negative,, whilst those with a score between 8 and 10 would have a 93% liklihood of having positive nodes. We wish to report the progress and findings at lymphadenectomy of a small group of patients presenting with apparently localised prostatic carcinoma.

Patients and Methods

A series of 16 patients with an average age of 65.6 years presented over a 2½-year period with clinically localised prostatic carcinoma (T1/T2). Histological

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confirmation and grading was obtained by resection biopsy or transrectal tru-cut needle biopsy and Gleason scores were assessed retrospectively by one of the authors (K.G.). These patients had undergone bone scan and CT of abdomen and pelvis to detect extracapsular spread and regional lymph node enlargement, since these initial investigations proved negative, staging lymphadenectomy was undertaken and common iliac, internal iliac, external iliac and obturator nodes were removed entirely and sent for paraffin histology. Those patients whose nodes were negative underwent a course of radical radiotherapy to prostate alone, whilst those with positive nodes were offered orchiectomy No anticoagulant prophylaxis was given to 15 of 16 patients, though they wore anti-embolism stockings during surgery and post-operatively until mobile. The patients were managed post-operatively by IV fluids and nasogastric suction until gut motility returned and an intraperitoneal suction drain was left *in situ* for 24 h.

Results

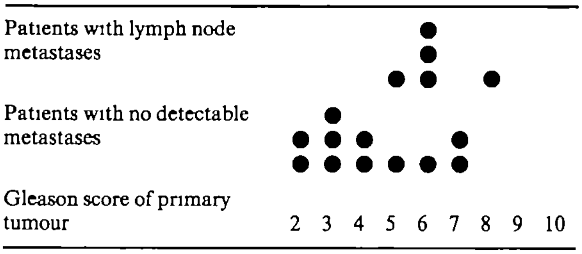
Five patients (32%) had positive nodes despite a negative CT scan. Histological examination showed that in those patients with involved nodes, the obturator group was positive without exception (Table 1). Comparison of Gleason scores on the original TUR material with node histology showed the same association of poorly differentiated tumours with positive lymph nodes noted by Grossman *et al.* (1980), although this relationship is insufficiently sensitive to predict nodal metastases with any certainty (Table 2). No patient died in the peri-operative period but 3 patients (20%) developed either a DVT (2) or pulmonary embolus (1) and required anticoagulation (Table 3). Average follow-up after lymphadenectomy was 22 months (range 10 months–3 years). All patients have an annual bone scan and to date no patient with a negative lymphadenectomy has developed bone metastases.

Table 1 Distribution of Involved Lymph Nodes

Patient	*Obturator*	*Internal iliac*	*External iliac*	*Common iliac*
LW	+	+	+	−
MW	+	−	+	−
CF	+	+	N/A	−
DH	+	+	+	+
PM	+	N/A	+	+

+ Metastases detected histologically.
− No histological evidence of metastases
N/A Histological assessment not available

Table 2 Relationship between Histological Grade (Gleason Score) of Primary Tumour and the Presence or Absence of Nodal Metastases as detected by Staging Laparotomy



Each mark (●) represents a single patient.

Table 3 Post-operative Complications Following Lymphadenectomy

	No of patients
Wound infection	1
Lymphoedema	0
Persistent lymph drainage	0
Thrombo-embolic event	3
Death	0
No significant morbidity	12
Total	16

Discussion

The only curative treatment options for localised prostatic carcinoma are either radical surgery or radiotherapy and the latter is currently the preferred treatment in the United Kingdom.

There is a significant acute and chronic morbidity associated with radical radiotherapy to the prostate and it is therefore essential that staging is completely accurate. Firstly, this will ensure that those with involved nodes are identified and patients spared the sequelae of inappropriate local treatment. Secondly, the small group of patients with high grade tumours, who might be expected to have lymph node involvement and to be offered hormonal manipulation, but in fact who prove to have histologically normal lymph nodes, can be given curative radical radiotherapy. It is noteworthy that 5 of 9 patients with Gleason score 5 and above were node-negative.

As this staging is critical, and given the insensitivity of CT scanning to detect tumour involvement in normal sized lymph nodes (Golimbu *et al.*, 1981), lymphadenectomy remains the only method of providing this information with sufficient accuracy.

There is a significant morbidity associated with lymphadenectomy, of which DVT and pulmonary embolus are the most serious; 3 of 15 patients without systemic prophylaxis developed significant DVT (2) and pulmonary embolus (1) requiring systemic anticoagulation. We feel it is important to give systemic prophylaxis, by way of low dose heparin, or systemic anticoagulation, despite the fact that Koonce *et al.* (1986) observed an increase in complications, particularly lymphocele, infection and haemorrhage following such a practice. Where a patient has a high likelihood of DVT or where anticoagulation cannot be exhibited, then lymphadenectomy is contraindicated. There have been no lymphoceles or peripheral lymphoedema of significance in our series. This may in part be due to the transperitoneal approach with no attempt being made to close the peritoneum over the great vessels.

It is likely that the extent of lymphadenectomy and dissection around the great vessels contributes to the risk of DVT. It is noteworthy that the obturator nodes were involved in all positive cases and that a limited lymphadenectomy to the obturator triangle may provide accurate information with reduction in the risk of thrombo-embolic complications.

Staging lymphadenectomy for clinically localised prostatic carcinoma is associated with significant morbidity, the most significant of which is thromboembolism. The advantages of lymphadenectomy include the detection of curable disease when the nodes are histologically free of metastatic disease, and the avoidance of radiotherapy and its often permanent sequalae when spread of tumour to the nodes is detected. It also allows the isolation of curable disease in patients with high grade lesions whose prostatic histology alone would suggest probable node involvement. Without the benefit of a negative lymphadenectomy, these patients might be denied curative therapy. Lymphadenectomy is not appropriate for those patients with a high risk of deep venous thrombosis or when anticoagulation is contraindicated.

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Prognostic Factors in the Surgical Treatment of Azoospermia

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Summary—Surgery for male obstructive infertility is not always successful. A number of clinical and operative findings, not previously reported, may influence the outcome. We have studied 182 patients with azoospermia who underwent vasoepididymostomy. The pre-operative and operative findings which adversely affected the function of the anastomosis were identified. The presence of spermatozoa in the semen sample was taken to mean a successful anastomosis. Abnormal testicular histology was an adverse pre-operative finding. Adverse operative findings included non-canalisation of the epididymal tubules and hypoplasia of the epididymis; both factors were associated with a high failure rate (almost 100%). The anastomosis was a failure in 78% of the patients when no fluid was seen on sectioning the epididymis. In the absence of adverse findings the success rate of vasoepididymostomy was 59%. Pre-operative testicular biopsy, together with careful observation and recording of findings before and during surgery, are recommended to avoid needless exploration and anastomosis.

Patients with azoospermia, normal serum FSH and normal semen fructose frequently have primary obstructive infertility. Azoospermic patients constitute 7 to 19% of all cases of male subfertility (Phadke *et al.*, 1973), but not all of these merit surgical exploration and vasoepididymostomy (VEA). It is difficult to predict the outcome prior to surgical exploration and uncertainty remains even after operation. The factors that influence the outcome have not been previously described. We have analysed 260 infertile male patients treated by surgery in order to identify the findings which consistently influence the outcome in patients with primary azoospermia.

Patients and Methods

All patients referred to the male infertility clinic had clinical parameters and investigations recorded on a standard proforma. Criteria of eligibility for operation included the presence of the following: infertility after 1 year of marriage, azoospermia, at least 1 testis larger than 15 ml and a clinically palpable vas. Clinical assessment of epididymal size on palpation was not a factor when considering patients for surgery. Vasograms were not done since vasography itself can cause vasal obstruction (Amelar and Dubin, 1982). Testicular biopsy was not usually performed; however, 246 patients had had testicular biopsies before referral to our clinic. If the testicular biopsy showed diffuse testicular atrophy (42 cases) the patient did not receive surgery, but if the biopsy showed hypospermatogenesis or foci of atrophy (52), or a normal testis (152), the patient was accepted if he otherwise fulfilled the criteria for surgery. All operations were performed as out-patient procedures under local anaesthesia. One side was operated upon, with the help of a Leitz OpMi 1 operating microscope. The patency of the distal vas was checked by injecting saline into the vas and free flow was taken to mean distal patency. If this was absent the procedure was abandoned. A 3 to 4-mm epididymotomy was made, cutting across at least 1 meander of the epididymis. A vasotomy of similar length was made distal (from the testis) to the obstruction. A side-to-side VEA using 6/0 prolene was carried out, anastomosing the vas to the edges of the epididy-

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motomy and not to an individual tubule of the epididymis. If the epididymis was very small, fibrotic or without tubules, no anastomosis was done. If only mild hypoplasia was present (epididymis less than half of the expected size but showing tubules on sectioning) or if it was normal or distended, an anastomosis was performed.

Semen analysis was done at 6 weeks and the presence of spermatozoa was taken to mean a patent anastomosis, regardless of sperm count.

Results

A total of 260 patients fulfilled the criteria for surgery and were explored. The age range was 22 to 42 years (mean 33). Vasoepididymostomy was abandoned in 52 patients. The vas, thought to be clinically palpable, was found to be missing on exploration in 23 patients. In 14 cases the epididymis was severely hypoplastic. In 13 patients there was distal obstruction of the vas and although the fluid from the proximal vas contained sperm, injection of saline resulted in increased tension in the vas with backflow of saline. In all of these cases an anastomosis was not performed. In 2 cases the surgical procedure had to be abandoned because of extensive adhesions following previous hydrocele surgery. Thus a VEA could be carried out in only 208 of the original 386 cases (54%); 182 of these were available for follow-up after 6 weeks.

The follow-up semen analysis showed spermatozoa in 62 out of the 182 patients in whom a VEA was performed (34%); 13 had normospermia and 49 had oligozoospermia (sperm count <20 million/ml). The earliest reappearance of sperm was at 6 weeks and the latest at 11 months; 6 patients progressed from oligozoospermia to normospermia over a period of 1 year.

The findings associated with a poor prognosis were analysed, as were those observed at surgery and on testicular biopsy.

Absent epididymal fluid. The absence of fluid on sectioning the epididymis usually indicated a poor prognosis but was not always associated with failure. Of 27 patients with this finding, 6 (22%) had a positive result.

Hypoplastic epididymis. An epididymis less than half of its expected size, but with tubules present, was considered for anastomosis. However, the anastomosis was never successful, even when the tubules in such an epididymis were patent, and the procedure failed in all 11 patients with this finding.

Solid epididymal tubules. Non-canalisation of the epididymal tubules was almost invariably associated with failure. Of 20 patients with this finding, only 2 had sperm positivity after VEA.

Testicular abnormality. Patients with hypospermatogenesis or focal areas of testicular atrophy also produced disappointing results. The operation was a failure in 17 of the 19 patients with this finding on histology.

Other findings. A thick inspissated fluid was found on sectioning the epididymis in 2 patients and the operation was a failure in both; 15 patients had more than 1 of the findings described above and in all of these the VEA was unsuccessful.

No unfavourable findings. In patients with none of these poor prognostic findings the VEA was patent in 59%.

Discussion

The use of the operating microscope has facilitated accurate anastomotic procedures with an increased probability of success. However, surgery in the treatment of male infertility continues to be disappointing and this is partly due to the absence of clearly defined contraindications. If criteria could be identified that are associated with a poor prognosis, a large number of unnecessary operations would be avoided. It is recognised that an anastomosis is not feasible in all cases and Wagenknecht (1982) stated that in 28% of his patients an anastomosis could not be made. Details of selection criteria have not been discussed before and the success rate has not been correlated with operative and pathological findings. Despite an initial screening which excluded from surgery almost 30% of the patients referred to us (Table), the anastomosis could not be performed in 52 (20%) of the patients accepted for operation. Our findings may help to improve the selection of patients for surgery and

Table Patients Excluded Pre-operatively

	No of patients
Small testes <15 ml	41
Severe testicular atrophy	42
Oligozoospermia	26
Vas not palpable	17
Total	126

lead to a more realistic anticipation of surgical success.

Clinical and pathological criteria

It is clinically possible to palpate the vas and no surgery was attempted in patients with bilateral absence of the vas. However, in a few cases it was impossible to be certain that the vas was truly missing on one or both sides and an exploration was carried out to give the patient the benefit of the doubt. In all, including the patients not operated upon because of a non-palpable vas and those in whom the vas was found absent at operation, the vas was missing in 10.4% of patients attending the sterility clinic. This is probably the most common developmental anomaly (Wagenknecht, 1982).

When the epididymis is clinically small the prognosis must be guarded. However, in our series all such patients were explored to confirm the size of the epididymis. Since a hypoplastic epididymis was almost always associated with failure, surgery should be avoided when the epididymis is clearly very small on both sides.

A pre-operative testicular biopsy was not performed in every case. In patients in whom it had been performed prior to referral it became clear that any testicular abnormality, in the form of arrest of maturation of spermatozoa or focal areas of testicular atrophy, was almost always associated with failure. Size is not an adequate indicator of histology. In patients with a testicular size between 10–14 ml, 40% had histologically normal testes; in those between 15 and 19 ml, 63% of testes were histologically normal. Above this size, 70% of testes were normal on histology. Since testicular abnormality has a very poor prognosis, a testicular biopsy should always be performed before operation. Infertile patients with normal sized testes may often have testicular defects and will not benefit from surgery.

Operative criteria

Sectioning the epididymis prior to anastomosis usually produced a turbid white fluid. It was found that if this fluid was absent, the results were worse. However, such a finding in itself should not be an indication for abandoning the procedure, for 22% of such anastomoses functioned well. The reason for success, despite the absence of fluid, is possibly due to the fact that not all meanders of the epididymis contain fluid under pressure.

The epididymal tubules were sometimes found not to be canalised. These solid tubules do not function and an anastomosis in these cases nearly always fails. If careful examination of the epididymis shows it to be blocked the procedure should be abandoned.

Absence of negative markers

When none of the "unfavourable" factors were present, the success rate in terms of a functioning anastomosis was nearly 60%. This compares well with the 30 to 70% patency rate reported by other workers (Lipschultz and Howards, 1983).

Infertile couples often wish to make a decision in terms of adoption or artificial insemination and an unnecessary procedure delays this decision and gives false hope. We suggest that surgery in primary azoospermia should be considered only if the vas is palpable, the epididymis is not felt to be smaller than half of its expected size, and testicular biopsy is normal.

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Hypogastric Plexus Stimulators for Obtaining Semen from Paraplegic Men

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Summary—Radio-linked devices to stimulate the hypogastric plexus have been implanted into 7 patients with spinal injuries and 1 with primary anorgasmia. They caused seminal emission in all patients and still do so in the spinal injury patients. Insemination with semen thus obtained has yielded 5 pregnancies (2 live births) in the wives of 4 patients. The range of application is discussed.

Some men with cervical or thoracic spinal cord injuries can ejaculate reflexly, though in most cases only if a powerful vibrator is applied to the penis (François *et al.*, 1980) or if physostigmine and metoclopramide are given in advance (Chapelle *et al.*, 1983). Some men with lesions of the lumbosacral cord have psychogenic seminal emissions and these emissions may suffice for fertility. There remain many men with damaged spinal cords from whom semen cannot be obtained by these means. For them, either electroejaculation (Brindley, 1981) or some kind of operative surgical intervention is required if they are to become fathers. One appropriate operative technique, the implantation of vas deferens cannulas and sperm reservoirs, was described by (Brindley *et al.* 1986a). We now describe another and specify its field of applications.

Principle

The hypogastric plexus can be seen with the naked eye as a network of nerve bundles running in front of the lower abdominal aorta, its bifurcation and the left common iliac vein (Fig. 1). This plexus carries most of the sympathetic supply to the pelvic organs. Isolated lesions of it are not rare. They can, for example, result from dissection of para-aortic lymph nodes in the treatment of testicular carcinoma. If complete, these lesions cause failure of

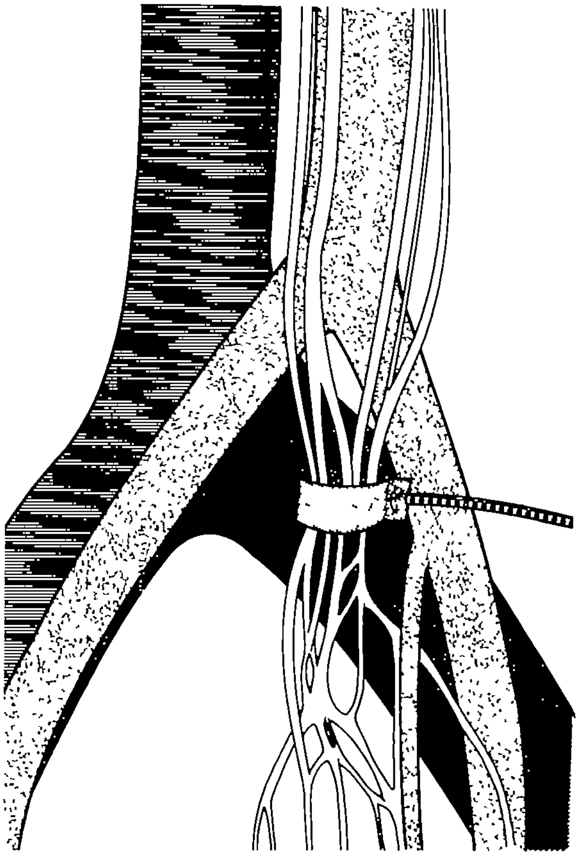

Fig. 1 The hypogastric plexus is trapped immediately below the bifurcation of the aorta.

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seminal emission, orgasm remaining normal or nearly normal.

One might expect from these facts that electrical stimulation of the hypogastric plexus would cause seminal emission. Experimentally, in monkeys, it does so, both under general anaesthesia (Brindley, 1981) and without anaesthesia (see below).

Implants

All implants were made in the MRC Neurological Prostheses Unit on the principles described by Donaldson and Sayer (1981) and Donaldson (1987). Figure 2 shows the most recent. The earlier implants differed only in minor details. The radio receiving circuit is the same as that of the sacral anterior root stimulator (Brindley *et al.*, 1986b). The cable is Cooper cable (Donaldson, 1983) made by Finetech Ltd (Welwyn Garden City). The plexus is stimulated unipolarly, with a remote indifferent electrode on the receiver block, except in patient 3, for whom tripolar stimulation is used.

The whole implant, except for the active and indifferent electrodes, is coated with a mixture of gentamicin, fucidin and silicone rubber (Rushton *et al.*, 1989).

The transmitters and their driving circuits are similar in most respects to those used with sacral anterior root stimulator, implants, but are simpler.

Implants and external equipment are not yet produced commercially but can be bought from the MRC Neurological Prostheses Unit.

Patients

The most important facts about these are given in the Table. The first radio-linked hypogastric plexus stimulators were implanted in 1980 into 2 New World monkeys of the species *Cebus apella*. Both monkeys were healthy and at least 5 years old.

The first human patient (1981) had primary anorgasmia. The 7 subsequent human patients (1983–1988) fulfilled the following criteria. All had traumatic spinal cord transections, complete in patients 2, 3, 5, 6 and 8, and slightly incomplete in patients 4 and 7. They and their wives wanted to have children. None of them could ejaculate in sexual intercourse, by masturbation or by Ling 201 vibrator at 80 Hz and 3 mm amplitude. In all 7 patients there was evidence of good survival of anterior and intermediate horn cells in the T10 to L2 segments of the spinal cord. All were believed pre-operatively to have no pain sensitivity depending on spinal roots below the ninth thoracic. For patient 7 this belief (which was based on examination by a neurologist) was found post-operatively to be erroneous.

Surgical Technique

In the 2 monkeys the plexus was trapped directly in front of the bifurcation of the aorta. In human patients a slightly lower site (Fig. 1) is used for the trap.

The abdomen is opened through a lower abdominal incision and the bowels are packed away. The

Table Details of Patients

Patient	*Lesion*	*Hypogastric stimulator implant*	*Age at operation*	*Best count (× 10^6/ml) and motility*	*Pregnancies*	*Notes*
1	Primary anorgasmia	Feb 1981	32	35 29%	Daughter 1982 Son 1984 (not by implant)	Use of implant severely painful
2	T9, 1968	July 1983	37	50 10%	2 spontaneous abortions	SARS
3	T9, 1982	Dec 1984	29	6 48%	1986 healthy daughter	SARS
4	C7 incomplete, 1973	May 1986	32	30 45%	1986 healthy daughter	BNR SARS
5	T3, 1976	Mar 1987	29	54 22%	1988 spontaneous abortion	BNR SARS
6	T4, 1973	Sept. 1987	32	4 8%	—	Needs desipramine
7	C5 incomplete, 1983	Sept 1987	31	2 0%	—	Use of implant painful
8	T5, 1985	Feb 1988	27	29 5%	—	

SARS = sacral anterior root stimulator BNR = bladder neck resection.

peritoneum overlying the bifurcation of the aorta is widely opened and the tissue lying in front of the lower end of the aorta is carefully dissected. This tissue does not look like a nerve in the classical sense, but resembles strings of fibrous tissue mixed with fat. This is collected from between the origin of the 2 common iliac arteries and gathered in a trap (Fig.2 upper right) which is placed around the tissue and secured with a silk ligature. To confirm that the plexus has been correctly identified, electrical stimulation at 10 V, 30 Hz, 350 µs is applied between the implanted electrode as cathode and a large indifferent anode. The 2 vasa deferentia are observed through the parietal peritoneum near the internal inguinal ring. Conspicuous contractions of both vasa should be caused by the stimulation.

The flexible cable (Fig. 2 left) that comes from the trap is passed behind the colon on either the left or the right side. On the right side it runs behind the right ureter and caecum; on the left side it runs behind the sigmoid mesocolon and the left ureter. The colon and ureter are allowed to fall back on top of the cable, which lies loosely in the posterior peritoneal tissues.

A subcutaneous pouch is made for the receiver over the lower ribs on the ipsilateral side and the cable is led to the receiver by means of a trocar and cannula.

The cable is connected to the receiver and the wounds are closed. Antiobiotic cover is given for 10 days.

Results

Monkeys

Each monkey had been previously taught to sit in a restraining chair. The results in both monkeys were the same. When the implant was activated by bringing a transmitter closer to the implanted receiver (the monkey sitting in its chair), emission of semen occurred without any indication from behaviour that the monkey was suffering pain. There was no erection.

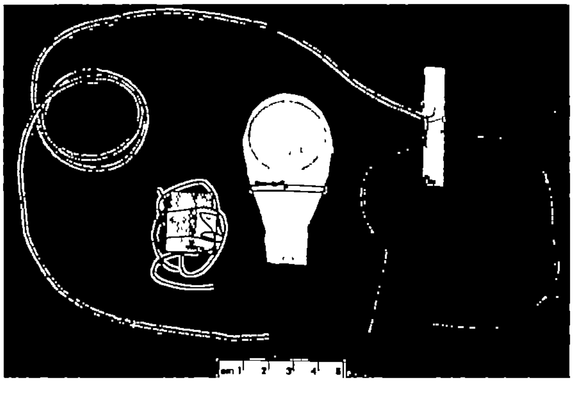

Fig. 2 The receiver (centre) and cable leading to the trap (right)

The semen coagulated to a firm solid within a minute of emission, as is normal for New World monkeys. Microscopic examination showed very many spermatozoa. In the firm coagulum they were non-motile.

The first patient (primary anorgasmia)

The first activation of the stimulator, 4 days after implantation, caused low suprapubic pain. The strongest stimulation that this pain allowed the patient to tolerate yielded no semen and caused no erection. Three days later, a second trial was done under general anaesthesia. Stimulation, at 15 Hz and about twice the voltage that had been used without anaesthesia, yielded 4 ml of semen containing 35 million spermatozoa/ml, motility 29%. It also caused full erection.

This patient's implant was never useful to him, though semen was obtained by it under general anaesthesia on 3 occasions in February and March 1981. In April of that year we discovered that prolonged application of the Ling vibrator to the patient's penis would trigger ejaculation. He subsequently fathered 2 healthy children by domestic artificial insemination with semen obtained in this way (1982 and 1984). In November 1986 the radio receiver of the implant and part of its attached cable were removed.

The 7 patients with spinal injuries

The implants were tested without anaesthesia a few days after the operation. In all patients external emission of semen occurred, the volume being between 1 and 5 ml in patients 2, 3, 7 and 8. In patients 4, 5 and 6 only a drop or two of semen was obtained at the first post-operative test, but good quantities were obtained later (see below).

Stimulation through the implant caused slight swelling of the penis in patients 2, 5 and 7, moderate swelling in patients 4 and 6, nearly full erection in patient 3 and full erection in patient 8.

Sensory effects in the spinal injury patients

Patient 4, who has good tactile and proprioceptive sensitivity over his whole body (though no pain or temperature sensitivity or voluntary movement below C7), experiences non-painful sensations which, he says, correspond closely to the contraction of lower abdominal muscles and flexion of the hips which can be seen to occur as a reflex consequence of the stimulation. Patients 2, 3, 5, 6 and 8 experience no sensations referred to parts of the body below their sensory levels, but the last 3 report mild sensations in the head and neck. These sensations do not begin until a few seconds after the onset of stimulation and continue for a few seconds (occasionally minutes) after stimulation has ceased.

Patient 7 has no voluntary movement below C5 level and his tactile sensitivity below this level is far more defective than that of patient 4. Preoperative examination by a neurologist revealed no pelvic sensitivity. However, when the implant was tested 1 day after operation and again 4 weeks after operation, hypogastric stimulation caused fairly severe lower abdominal pain. On both trials about 1 ml of normal-looking semen was obtained, containing a few non-motile spermatozoa. Re-examination then showed that though the patient failed to discriminate the sharp from the blunt end of a pin for single pinpricks in the upper lumbar dermatomes, multiple pinpricks were detected reliably and perceived as painful.

Fourteen weeks after the operation, hypogastric stimulation was done after intrathecal injection of lignocaine through the space between the T12 and L1 vertebral laminae. The injection caused loss of the previously present lower abdominal cutaneous reflexes, diminution but not loss of the knee jerks, and alteration of the response of scratching the soles of the feet from extension of the toes with hip flexion to extension of the toes only. In this state, hypogastric plexus stimulation caused no pain at all. It yielded 1 ml of normal-looking semen containing a few non-motile spermatozoa.

Eleven months after the operation, hypogastric plexus stimulation was again tried without spinal anaesthesia. It yielded semen containing non-motile spermatozoa with only slight lower abdominal pain. The implant is now in regular use.

Long-term results

Reliability of the implant. In April and June 1987 the implants of patients 5 and 2 failed. In both cases we suspected that the fault was in the passive radio receiver. We replaced both receivers (a simple surgical procedure) and both implants are now functioning again. The fault in patient 5 was in the soldered connexion at one end of the coil. In patient 2 the diode had failed. We have since improved the soldering technique and the implants of patients 6 to 8 have two diodes in series to ensure that their inverse voltage rating is never exceeded. The radio receiver that was removed from patient 1 after remaining unused for 5½ years was in good working order when tested a few days after removal.

The implants of all 7 spinal injury patients have continued to yield semen containing spermatozoa (of which usually but not always some were motile) for periods of 5, 4, 2½, 1½, 1, 1 and ½ years.

Bladder neck resections. Patients 4 and 5 already had bladder neck resections and sacral anterior root stimulation implants. In both patients, use of the hypogastric stimulator alone yields partly or wholly retrograde emission. Patient 4 finds that his best technique for getting semen is to operate the hypogastric stimulator and then the sacral anterior root stimulator. The first usually yields nothing externally, the second a stream of liquid of which the first 2 ml appears to be pure semen, but the rest mainly urine. His wife has become skilful at catching the semen. Patient 5 has used the same technique, but now prefers to use the hypogastric stimulator when the bladder is about two-thirds full. It then usually yields semen externally. With a less full bladder, nothing is obtained externally, with a fuller bladder a mixture of semen and urine.

Noradrenaline re-uptake blockers to improve performance. In men with incomplete lesions of the hypogastric plexus, a noradrenaline re-uptake blocker, either imipramine (Brooks *et al.*, 1980) or the more specific desipramine (Brindley, 1986), will often convert non-ejaculation or retrograde ejaculation into external ejaculation. Patient 6 needs this. If he takes desipramine 75 mg 2 h beforehand, hypogastric plexus stimulation by implant regularly yields 1 ml of more of semen externally. Without desipramine, it gives only retrograde emission.

Quantity and quality of semen. By analogy with the consequences of repeated electroejaculation in men who have not ejaculated for years (Brindley, 1983), we hoped that the volumes, the counts and especially the motilities would improve during the first few months after implantation of the stimulator. Some patients have shown such improvements, but they have been disappointingly small. The longest follow-up is for patient 2. The most recent trial of his implant in November 1988 yielded 4.8 ml of normal-looking semen containing only 10 million spermatozoa/ml, all non-motile. However, this patient produced specimens containing no motile spermatozoa in August 1983 and March 1985, though the majority of his specimens have had motilities between 5 and 10%. There is no clear long-term trend either upward or downward in count or motility in him or in any other patient.

Pregnancies. The 2 children fathered by patient 1 in 1982 and 1984 show merely that his useless hypogastric stimulator did his fertility no harm. The daughters of patients 3 and 4, both fine healthy children (the latter talking in whole sentences at the age of 19 months), constitute the only real successes of the procedure at the time of writing. The wife of patient 2 is now aged 40, so future success is unlikely for this couple. The fertility of patient 5 and his wife is proved by their one pregnancy and future success for them is likely. Patients 6 and 8 may perhaps succeed. A success for patient 7, with no motile spermatozoa yet seen, seems very unlikely, now that we know from the other patients that the establishment of regular drainage of semen does not lead to large improvements in its quality.

Discussion

All 8 implants have produced semen and there has been no morbidity. Implants continue to function for years without deterioration in their performance.

Field of application

The experience of patients 1 and 7 shows that men who retain significant pelvic pain sensitivity are unsuitable This excludes men with primary anorgasmia, even if the powerful vibrator with drug supplementation (Brindley, 1984) has been tried and fails, because electroejaculation under general anaesthesia provides a fairly good remedy for their infertility, without the need for implantation of a stimulator. Among men with spinal injuries, inability to distinguish the sharp from the blunt end of a pin may not exclude significant pain sensitivity, as the experience with patient 7 shows. An attempt at electroejaculation without a general anaesthetic is almost sure to be an adequate test. If it is tolerated, hypogastric plexus stimulation by implant will be tolerated. The same test incidentally allows patients with severe autonomic dysreflexia to be identified and excluded. We now think that electroejaculation is a necessary preliminary test, and probably patients from whom it yields semen containing no motile spermatozoa should be excluded.

Survival of the cells of origin of the preganglionic pelvic sympathetic fibres is a requirement. The cells lie in the intermediate horns of grey matter of (probably) the T10 to L2 segments of the spinal cord. Their survival is probable in all patients with cervical or upper thoracic spinal injuries, and in those patients with lower thoracic injuries for whom each hip flexes on scratching the sole of the corresponding foot. Successful electroejaculation (which is needed as a preliminary for other reasons) suffices to prove that they survive.

Patients who are unable to ejaculate because of lesions of the spinal cord or cauda equina, but are unsuitable on the above criteria for a hypogastric plexus stimulator, are generally suitable for vas deferens cannulas and sperm reservoirs, provided that testicular and epididymal function survives.

Implantation of a hypogastric stimulator is unjustified if a simpler and equally convenient method of obtaining semen is available. Therefore all patients must be tested by application of a powerful vibrator to the glans penis; if this yields semen, it is clearly preferable. Electroejaculation is probably not preferable, since semen can be obtained by it only by an expert user with access to expensive equipment. Given the poor quality of most paraplegic semen (and therefore the need for many inseminations), electroejaculation is a troublesome and inconvenient method of achieving a pregnancy in the wife of a paraplegic man. Opinions will differ as to whether one ought to try Chapelle's physostigmine technique before resorting to operative surgery to enable a paraplegic man to have children. When it succeeds, Chapelle's technique is less troublesome than electroejaculation, but more troublesome than vibrator application.

All patients suitable for hypogastric plexus stimulators are suitable also for vas deferens cannulas and sperm reservoirs. Where either procedure would work, we think the hypogastric plexus stimulator is always preferable. Though slightly more complex surgically, it yields better semen, containing the prostatic and vesicular components as well as the testicular and epididymal. A hypogastric plexus stimulator, if it works initially, is almost sure to go on working for 15 years. There is no such assurance for cannulas and reservoirs.

The hypogastric plexus stimulator is a good means of achieving fertility in men with spinal cord lesions above about T9 who do not have reflex ejaculation, whose lesions are complete or spare only the posterior columns, and in whom most of the intermediate horn cells of the T10 to L2 segments survive.

Such patients can use the semen obtained for implant for AIH done at home without medical help.

An incompetent bladder neck is no contraindication, provided that the patient has a sacral anterior root stimulator implant.

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Morphology of Testicular Germ Cell Tumours in Treated and Untreated Cryptorchidism

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Summary—The histology of 75 testicular germ cell tumours in 73 patients with treated or untreated cryptorchidism was investigated in a group of 503 patients with testicular germ cell tumour and evaluated according to the WHO classification. The proportion of pure seminoma was associated with the height of the testis, being 87% in abdominal. 78% in inguinal and 50% in normally positioned testes. In patients operated upon for cryptorchidism. the current site of the testis seemed to be a more important determinant of this proportion than the original site. The proportion of pure seminoma which developed in testes after successful orchiopexy was equal to that in normally-descended testes (50%) and lower (39%) if orchiopexy had been performed before the age of 16 years. Similarly, among non-seminomas, a higher proportion of tumours containing teratoma tissue was found if cryptorchidism was successfully treated in childhood. It was concluded that a successful orchiopexy in childhood decreases especially the risk of seminoma.

Anamnestic or prevalent cryptorchidism is a well known risk factor in the development of testicular germ cell tumours. The risk has been estimated to be 15 to 40 times that of a scrotal testis and even higher in a subgroup of abdominally situated testes (Batata, 1976; Martin, 1982). The mechanism that leads to an increased risk of cancer in a cryptorchid testis is unclear. The histological changes that take place in a malpositioned testis, or the defects in the mechanisms that regulate testicular descent, may render the testis more susceptible to cancer. Whether or not the risk of cancer can be reduced by orchiopexy is still unresolved.

Orchiopexy has various effects on the histology of the testis, *e.g.* the spermatogenic tissue develops more normally if orchiopexy is done during the first years of life. Analogically, it can be asumed that tumours which develop in testes after orchiopexy are histologically different from those which develop in testes left in the cryptorchid position.

The factors that influence the pathogenesis and differentiation of testicular tumours are not well known but involve a common multipotential stem cell capable of differentiating in various directions (Dixon and Moore, 1952; Teilum, 1965; Mostofi and Sesterhenn, 1985). The concept of intratubular germ cell neoplasm (carcinoma *in situ*) found, for example, in testes of cryptorchid (Skakkebaek and Berthelsen, 1982) and infertile patients (Skakkebaek, 1978), and considered to be a precursor of invasive germ cell tumours (Skakkebaek and Berthelsen, 1981), is well established.

Seminoma is common in cryptorchid testes (Batata, 1975; Martin, 1982) compared with unselected sites in which the proportion is close to 50% (Teppo, 1973; Stalsberg *et al.*, 1983; Krag Jacobsen *et al.*, 1984). On the other hand, the proportion of seminoma among tumours that have developed after a successful orchiopexy is lower (below 50%) (Batata *et al*, 1982; Martin, 1982). The aim of this study was to analyse and compare the histology (Mostofi and Sobin, 1977) of testicular tumours in patients with both treated and untreated cryptorchidism rather than to assess the risk of testicular cancer among patients with different types of cryptorchism.

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Patients and Methods

The basic patient population consisted of all adult testicular germ cell tumour (GCTT) patients diagnosed in Finland between 1970 and 1982 and recorded in the Finnish Cancer Registry (473 cases, mean age 36 years). In addition, all new GCTT patients seen in the 5 University Hospitals in 1983 (28 cases) and in the 2 largest University Hospitals (in Helsinki and Turku) in 1984 and 1985 (32 cases) were included. The Cancer Registry files include practically all testicular tumours diagnosed in Finland (Teppo, 1973). However, the 28 cases from 1983 comprised about 80%, and the 32 cases from 1984 to 1985 about 45% of all GCTT patients diagnosed in Finland in those particular years.

For comparison, 43 non-germinal testicular tumours (NGCTT) (mainly lymphomas) registered in the Finnish Cancer Registry between 1970 and 1982 were also evaluated.

The hospital records of both the GCTT and NGCTT patients were evaluated in respect of anamnestic or prevalent cryptorchidism. This evaluation was based on the patient's history, physical examination and orchiectomy, the operation notes concerning possible previous orchiopexy and the findings concerning intra-abdominal testes and tumours in conjunction with laparotomy. A patient was described as cryptorchid if he had, or had previously had, cryptorchidism (ipsilateral and/or contralateral), either treated or untreated. The age at orchiopexy and the site of the cryptorchid testis were also recorded (Scorer and Farrington, 1971).

The term "current site" refers to the site of the testis at the time of orchiectomy because of tumour. "Original site" refers to the site of the testis before orchiopexy (or before spontaneous late descent in 1 patient) or the present location should no change have occurred. A testis was regarded as normally descended if it was scrotal at the time of tumour diagnosis and there was no anamnestic or other evidence of earlier cryptorchidism. Patients for whom hospital records were not available and for whom information was insufficient were excluded. A total of 503 patients (94% of the original material) with 510 tumours (7 bilateral) were included in the study.

The histological specimens of the 75 tumours found in 73 patients with cryptorchidism were collected from 21 laboratories around the country and reviewed and reclassified by a pathologist with special experience of testicular tumours (L.T.). In most instances the original slides were regarded as being adequate for analysis but in 10 cases new slides were prepared from paraffin-embedded tissue. A mean of 5 slides from various parts of the tumour was available. Tissue from 72 of the 75 tumours was obtained for reclassification; for the others the original histological diagnoses were used.

The WHO classification (Mostofi and Sobin, 1977) was followed and all tissue components were recorded. The tumours were initially divided into 2 main groups: pure seminomas (including spermatocytic seminomas) and non-seminomas. Non-seminomas were further divided into 2 subcategories: (1) those containing teratoma tissue (mature or immature, regardless of size), alone or in combination with any other component, and (2) other non-seminomatous tumours (*i.e.* embryonal carcinomas, yolk sac tumours, choriocarcinomas and mixed tumours without a teratoma component). The tumours of non-cryptorchid patients were not reviewed histologically. When the reclassified diagnoses of tumours of cryptorchid patients were compared with the original diagnoses with regard to the 2 main subgroups only, pure seminomas and non-seminomas, a change was required in only 1 instance. Hence comparison between the histological types of the cryptorchid (reclassified) and not-cryptorchid (not reclassified) GCTTs was considered satisfactory for these 2 main categories.

The statistical significance of the differences between 2 frequencies was tested by the chi-squared test.

Results

Of all GCTTs, 269 (52.7%) were seminomas and 241 (47.3%) were non-seminomas; 73 patients (14.5%) had, or had previously had, cryptorchidism (either ipsilaterally, contralaterally or on both sides), whereas only 1 of the 43 patients (2.3%) in the NGCTT group had, or had ever had, cryptorchidism ($P<0.05$). Two patients had a bilateral tumour, resulting in a total of 75 GCTT tumours in 73 cryptorchid patients.

Testicular retention was, or had been, right-sided in 27 patients, left-sided in 22 and bilateral in 24. The unilateral tumours of cryptorchid patients were more often on the left side (40/71; 56%), which deviates from the laterality of tumours in normally descended testes (191/435; 44% left-sided). Nine tumours (12%) developed within a normally descended testis with contralateral cryptorchidism, including 3 in retractile testes.

A total of 53 cryptorchid testes in 38 patients had been treated surgically. The age at orchiopexy ranged from 1 to 44 years (median 13); 14 operations had been done at the age of 16 or more. Only 3 had been carried out between the ages of 0 to 5 years. Most of the operations (64%) had been performed in the 1950s or 1960s. A total of 35 (66%) of the operated testes were in a scrotal position at the time of tumour diagnosis.

The histology of the 75 tumours in cryptorchid patients is given in Table 1. In 57 of the 72 reclassified tumours (79%) only 1 morphological component was found. In others there were 2 or more components.

Table 2 gives the histology of tumours of cryptorchid and non-cryptorchid patients in relation to the original site of the involved testis. There is a significant difference in the proportion of seminomas between cryptorchid and non-cryptorchid patients ($P<0.001$) and a correlation was found between the original level of the testis and the proportion of seminomas: 88% in abdominal, 64% in inguinal and 50% in normally descended testes. Of the 9 tumours which developed in a normally descended testis when the contralateral testis was cryptorchid, 5 were seminomas and 4 were non-seminomas.

The histology of the tumours in cryptorchid patients in relation to the current site of the involved testes is presented in Table 3. The proportion of seminoma in testes which were scrotal at the time of tumour diagnosis (17/33; 52%) was close to that in normally descended testes (50%).

Table 1 Histology of 75 Tumours in Patients with Anamnestic or Current Cryptorchidism

*Histology**	*No of tumours*
Tumours with 1 component (n = 57)	
S	48
EC	6
T	2
YS	1
Tumours with 2 or more components (n = 15)	
EC+T	5
EC+T+S	3
EC+S	2
EC+T+YS	2
EC+YS	1
T+CH	1
EC+T+CH+carcinoid	1
Tumours not reclassified (n = 3)	
S	2
EC	1
Total	75

*EC = embryonal carcinoma T = teratoma. S = seminoma. YS = yolk sac tumour CH = choriocarcinoma.

The proportion of seminoma (39%) among tumours which developed in originally inguinal but, after a successful orchiopexy before adulthood, currently scrotal testes differed significantly ($P<0.01$) from that (23/29; 79%) among tumours in originally inguinal testes with different subsequent fates, *i.e.* tumours which developed in testes for which no orchiopexy had been done or for which orchiopexy had been performed at 16 years or older, or for which orchiopexy had been carried out unsuccessfully (Table 4). Among the 9 patients with contralateral cryptorchidism, correction had been done in none of the 5 seminoma patients and in 3 of the 4 non-seminoma patients.

A similar trend was found in the frequency with which teratoma tissue was found in the non-seminomatous tumours which developed in originally inguinal testes (Table 5), teratoma being more usual and more often the dominating component when a successful orchiopexy had been performed before adulthood.

Among the 13 patients with bilateral inguinal cryptorchidism there were 5 in whom orchiopexy on both sides had been done before 16 years of age. Only 1 of these developed a seminoma, while 5 of the other 8 patients developed a seminoma.

Discussion

Testicular descent is a complex mechanism influenced by hormonal (Hadziselimovic, 1985) and anatomical factors (Forest, 1982). Arrest can occur at various levels of normal descent, or the testis can choose an ectopic route (Hezmall and Lipschultz, 1982). It is not clear whether the risk of cancer can be reduced by early correction of the anatomical position (surgically when hormonal therapy fails), and if the risk depends on the age at which orchiopexy is carried out. In a recent report, no correlation was found between the age at orchiopexy and subsequent risk of testicular cancer (Pike *et al.*, 1986).

The benefit of early orchiopexy on fertility seems to be better established. Histological changes, especially in spermatogenic tissue, take place in cryptorchid testes before the age of 2 years and these changes become more marked with time (Hezmall and Lipshultz, 1982; Hadziselimovic, 1985). Orchiopexy reduces the risk of deterioration and subsequent infertility (Chan *et al.*, 1982), especially if done during the first years of life (Hadziselimovic, 1985). There is evidence that not only the anatomical position, but also an intrinsic factor associated with cryptorchidism, are respons-

Table 2 Histology of 510 Germ Cell Tumours Diagnosed in Finland 1970–1985 according to Original Site of Testis

	Seminoma		*Non-seminoma*		*All*
Original site of testis	*No*	*(%)*	*No*	*(%)*	*No*
Abdominal	14	(88)	2	(12)	16
Inguinal	30	(64)	17	(36)	47
High scrotal	1		1		2
Retractile	–		1		1
Scrotal (contralateral cryptorchidism)	5	(56)	4	(44)	9
Both testes normally descended	219	(50)	216	(50)	435
Total	269	(53)	241	(47)	510

Table 3 Histology of 75 Testicular Germ Cell Tumours in Patients with Cryptorchidism according to Current Site of Testis

	Seminoma		*Non-seminoma*		*Total*
Current site of testis	*No*	*(%)*	*No.*	*(%)*	*No*
Abdominal	13	(87)	2	(13)	15
Inguinal	18	(78)	5	(22)	23
High scrotal	2		1		3
Retractile	–		1		1
Scrotal, originally cryptorchidism	12	(50)	12	(50)	24
Originally scrotal, contralateral cryptorchidism	5	(56)	4	(44)	9
Total	50	(67)	25	(33)	75

Table 4 Histology of 47 Tumours Located in Originally Inguinal Testes in Relation to Treatment by Orchiopexy

	Seminoma		*Non-seminoma*		*Total*
Treatment	*No*	*(%)*	*No*	*(%)*	*No.*
Successful orchiopexy at 0–15 years	7	(39)	11	(61)	18
Unsuccessful orchiopexy at 0–15 years	6	(86)	1	(14)	7
Orchiopexy at 16+ years	5	(83)	1	(17)	6
No orchiopexy	12	(75)	4	(25)	16
Total	30	(64)	17	(35)	47

ible for the changes in histology (Hezmall and Lipschultz, 1982).

In the present series, the difference in the proportion of cryptorchidism between patients with germ cell tumours and those with other testicular tumours favours the concept that the increased risk of cancer in cryptorchid testes involves mainly germ cell tumours. Hence it is the incidence of these tumours only that we can expect to reduce by orchiopexy.

Most of the orchiopexies had been done in the 1950s and 1960s, when patients with cryptorchidism received surgery at a later age than would be recommended today, but exact information about the age distribution at the time of operation for the whole country is not available. The fairly high median age at operation (13 years) and the fact that 25% of the operations had been done on patients aged 16 or more indicate that, in the present series, patients undergoing orchiopexy at a later than average age are over-represented. In particular, the proportion of unsuccessful operations (34%) is much higher than would be expected. In a follow-up study of 93 operated cases of cryptorchidism from the same period in Finland (Hortling *et al.*, 1967), there were only 2 anatomically unsatisfactory results. This suggests that a successful orchiopexy will reduce the risk of cancer.

Table 5 Histology of 21 Non-seminomatous Tumours in Cryptorchid Testes according to Level of Cryptorchidism

	Tumours with teratoma tissue	*Others*	*Total*
	No	*No*	*No*
Abdominal cryptorchidism	–	2	2
Inguinal cryptorchidism with unsuccessful or delayed orchiopexy	3*	3	6
High scrotal, no operation	1	–	1
Retractile, no operation	1	–	1
Inguinal cryptorchidism, successful orchiopexy at 0–15 years	8*	3	11
Total	13	8	21

*In 1 tumour only a focus of teratoma was found

Because many germ cell tumours are mixed, detailed histological comparisons are complicated and we focused on the proportion of pure seminomas among all tumours and on the proportion of teratoma-containing tumours among non-seminomas. Seminoma and teratoma have a different pathogenesis and rarely coexist when other components are not present (Mostofi, 1973); this contrasts with the frequent occurrence of teratoma and embryonal carcinoma in the same tumour ("teratocarcinoma") and seminoma, unlike teratoma, does not exist in childhood (Mostofi and Sesterhenn, 1985).

There is a correlation between the probability of a tumour being a seminoma and the original level of testicular descent. However, this probability seems to correlate more closely to the level of the testis at termination in childhood and is thus influenced by surgical correction of its position. Almost all tumours in abdominal testes were seminomas, as were most of the testicular tumours remaining in the inguinal position, but less than one half of the tumours which developed in testes where successful orchiopexy had been performed before adulthood were seminomas.

One explanation would be that orchiopexy influences the mechanism of tumour genesis and differentiation. If the normal anatomical position is restored by orchiopexy and the development of a testis thus returns to normal, the processes that take place in a growing tumour resemble those in tumours in initially scrotal testes. It appears that if orchiopexy is performed after a certain age, the "code" of the histological types of a subsequent tumour no longer changes, resulting in a distribution similar to that found in a malpositioned testis.

The incidence of cryptorchidism, which is the greatest risk factor for germ cell tumours, has been reported to be increasing (John Radcliffe Hospital Study Group, 1986). Accordingly, the incidence of testicular cancer is increasing in many areas of the world (Stalsberg *et al.*, 1983). If orchiopexy does not lessen the total risk of developing testicular germ cell tumours, it would suggest—in the present series—that it influences only the histology of subsequent tumours, favouring the more aggressive types. It is more likely, however, that the risk of all types of GCTT is reduced after a well timed orchiopexy; the probability that a developing tumour is a pure seminoma will decrease but the probability that it contains teratoma tissue will increase.

It should be noted that the groups compared in this study were not exactly similar, *e.g.* the initial anatomical situation of the testis in patients whose operations were successful may have been different from that in patients who were unsuccessfully treated, possibly reflecting a more severe defect in the mechanism of cryptorchidism. There may also be differences between patients who had orchiopexy and those who did not. Since a randomised study is not possible, caution is needed in the interpretation of the results.

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Neurophysiological Aspects of Penile Erection: the Role of the Sympathetic Nervous System

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Summary—Recent studies have revealed that the initiation, maintenance and rigidity of penile erection are under parasympathetic and somatotopic control. The mechanism of penile detumescence is still under debate. Single and combined cavernous and hypogastric nerve stimulation was used to study the influence of the sympathetic nervous system on penile erection and to indentify the mechanism of penile detumescence.

Penile arterial flow and intracorporeal pressure recordings during various stimulation patterns indicated that erection induced by stimulation of the cavernous nerve could be blocked by excitation of the upper hypogastric nerves. Venous outflow studies demonstrated that the inhibitory effect of the sympathetic nervous system was due to active vaso- and corporeal smooth muscle constriction. It was concluded that subsidence and suppression of erection is a sympathetic function.

Previous studies have shown that the neurophysiology of erection can be explained by 3 major inhibitory (sympathetic). Our findings are of clinical importance, since a better appreciation of the basic erectile mechanism is essential for successful management of erectile dysfunction.

The rapid progress in basic research of the anatomy, physiology and pharmacology of penile erection and the introduction of intracavernous injection of vasoactive agents for the diagnosis and treatment of impotent men by Virag (1982) have changed our understanding of erectile dysfunction (Newman and Northup, 1981; Brindley, 1983; Lue *et al.*, 1983a, 1987, Zorgniotti and Lefleur, 1985; Jünemann *et al.*, 1986a, 1987a and b; Lue and Tanagho, 1986; Fournier *et al.*, 1987; Jünemann, 1988). Intensive clinical investigations have resolved some of the controversy regarding the aetiology of erectile failure. Until the early 1980s, classical teaching held that more than 90% of impotence was psychogenic in origin. Recent clinical studies have indicated that at least 50% of these patients are impotent for organic reasons (Stief *et al.*, 1986; Virag *et al.*, 1986; Buvat *et al.*, 1987; Lue *et al.*, 1987; Padma-Nathan *et al.*, 1987; Wespes and Schulmann, 1987; Jünemann *et al.*, 1988). This demanded a new aetiological classification of erectile dysfunction into either organic or psychogenic. A further subdivision of the organic group occurs according to arterial, venous and neurological pathology (Persson *et al.*, 1988). The difficulties that remain in the discrimination between neurogenic and psychogenic impotence are partly due to our lack of understanding of erectile neurophysiology.

Since Eckhardt (1863) stimulated electrically the nervi erigentes in dogs and thereby induced an erection, the prevailing theory has been that penile erection is mainly a parasympathetic phenomenon. Semans and Langworthy (1938) demonstrated that the sympathetic nervous system plays an important role in the sexual function of the cat, particularly in the subsidence of erection. Further studies revealed that the integrity of the lumbar sympathetic chain

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is crucial for a normal erectile mechanism (Whitelaw and Smithwick, 1951). The clinical significance of the adrenergic component was confirmed by studies on sexual function. However, the findings were controversial (Klinge and Sjøstrand, 1977; Domer *et al.*, 1978; Melman and Henry, 1979; Newman and Northup, 1981). Although it became clear that the initiation and maintenance of penile erection were primarily under parasympathetic control, and cessation of tumescence was probably a sympathetic function, the precise mechanism of neurological control remained undefined. A new approach to the neuroanatomy and physiology of erection in dogs and monkeys (Lue *et al.*, 1983a and b, 1984a and b) advanced the understanding of erectile function and its controlling systems. This has since been complemented by further studies (Jünemann *et al.*, 1986b, 1987a and b; Jünemann, 1988). It became clear that stimulation of the parasympathetic and somatic nerve fibres of the penis in the correct sequence caused maximum erection with full rigidity (Jünemann *et al.*, 1987b). The influence of the sympathetic nervous system on the erectile response and the process of detumescence remains debatable.

We therefore designed an animal study on the effect of sympathetic nerve stimulation on penile erection in order to define the mechanism of detumescence.

Material and Methods

In 6 male mongrel dogs (weighing 23 to 25 kg), cuff electrodes were implanted around defined nerve structures to study the effect of electrostimulation of the parasympathetic and sympathetic nervous system on penile erection. Anaesthesia was induced with acepromazine (0.05 mg/kg bw) and ketamine (5.0 mg/kg bw) subcutaneously, followed by intravenous boluses of sodium pentobarbital (60–90 mg) to maintain an adequate level of anaesthesia and spontaneous respiration. Fluid was maintained by the intravenous infusion of normal saline solution (2 ml/kg/h). On completion of surgery and correct placement of all monitoring devices, each animal was anticoagulated with an intravenous 1000-u bolus of sodium heparin and maintained with 50 u/h to avoid clotting in the pressure recording cannulae.

Surgical procedure

The animal was placed in a supine position and the entire abdominal and genital area shaved. Through a midline incision the bladder, bladder neck and prostate were exposed; the cavernous nerve bundle on the dorsolateral aspect of the prostate gland was identified by intra-operative neurostimulation and a cuff electrode (Avery Laboratories) placed around the right cavernous nerves to induce an erection by electrostimulation (Lue *et al.*, 1983a; Jünemann *et al.*, 1986b). An ultrasonic blood flow probe (Transonic Systems, Ithaca, USA) was placed around the internal pudendal artery, caudal to the branching of the urogenital artery (Christensen, 1954) to measure blood flow to the penis. Slightly below the hypogastric plexus, anterior to the aorta, the sympathetic nerve fibres deriving from the lumbar roots L2 to L5 were carefully dissected and a second cuff electrode placed around both upper hypogastric nerve bundles, enabling additional stimulation of the sympathetic nervous system (Fig. 1).

The entire penis was denuded, exposing the glans penis and both corpora cavernosa down to the ischial rami. Two 21-gauge butterfly needles were placed proximally into each corpus cavernosum and connected to a Statham pressure transducer for intracorporeal pressure recording. A third butterfly needle was inserted into the distal portion of the right cavernous body for controlled saline perfusion of the penis (Harvard perfusion pump), thus enabling us to study the venous outflow system of the penis by clamping the aorta and perfusing the penis with saline at a constant flow rate (1.9–7 ml/min) with and without neurostimulation (Jünemann *et al.*, 1986b).

Blood pressure, monitored through a 16-gauge cannula placed in the femoral artery, intracorporeal pressure and penile blood flow were measured simultaneously before, during and after each neurostimulation trial. A 10-minute interval between each neurostimulation procedure allowed the erectile tissue and autonomic nervous system to recover.

To study the influence of the sympathetic nervous system on penile erection, the following *in vivo* experiments were designed.

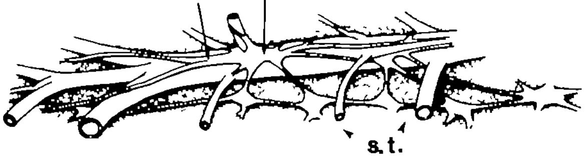

Fig. 1 Neuroanatomy of sympathetic trunk (s t) and nerve fibres forming the hypogastric nerve (h.n.) in the dog The cuff electrode was placed around the upper hypogastric nerve, just below the caudal mesenteric ganglion (c.m.g)

Arterial Inflow Studies

Single nerve stimulation

Baseline readings for arterial inflow to the penis, systemic blood and intracorporeal pressure, with and without single cavernous nerve stimulation and during sympathetic nerve excitation, were performed separately. Each trial lasted 2 to 3 min.

In all 6 dogs tested the cavernous nerve bundle was stimulated twice: first, with the individual threshold voltage (0.5–2.5 V/20 Hz) and subsequently with a higher amplitude (1.2–4 V/20 Hz); for sympathetic stimulation a higher voltage was applied (14 V/20 Hz).

Combined cavernous and sympathetic nerve stimulation

Once the threshold parameters for single nerve stimulation were obtained, the erectile response to combined cavernous and upper hypogastric nerve stimulation was measured. Two different modes were used.

1. Cavernous stimulation was applied until full erection was achieved and maintained at a high intracorporeal pressure plateau for 1 min, before additional neurostimulation of the sympathetic nerve fibres was initiated. The combined stimulation was continued for 1 min, or until the intracorporeal pressure dropped significantly. Subsequently, hypogastric stimulation was terminated while the cavernous nerve fibres were kept activated for an additional 2 to 3 min.
2. Hypogastric neurostimulation was applied 1 min prior to cavernous stimulation and maintained for 1 additional min before being terminated. Cavernous stimulation was continued for a further 2 min, as in the previous study.

Venous Outflow Studies

Single nerve stimulation

On completion of the arterial inflow studies the venous outflow system of the penis was evaluated during cavernous nerve stimulation by clamping the aorta and perfusing the corpora cavernosa with normal saline at a constant flow rate with and without neurostimulation (see above). Intracorporeal pressure change and time until half of the maximum pressure scale was passed ($T_{max/2}$) were recorded.

Combined cavernous and sympathetic nerve stimulation

Only the first of the 2 stimulation modes was used. After 1 min of corporeal perfusion with normal saline, electrostimulation of the cavernous nerve bundle was initiated (2–8 V/20 Hz). When the intracorporeal pressure reached 70 cm H_2O the hypogastric nerve was activated and maintained until the pressure in the corpus cavernosum decreased significantly. Cavernous stimulation was continued for 3 min after termination of the hypogastric stimulation. Intracorporeal peak pressure, corporeal pressure drop and time until detumescence were monitored.

In all studies the stimulation parameters remained the same, defined by single nerve stimulation. The erectile response to cavernous nerve stimulation was used as the maximum penile erection of each dog studied. Statistical analysis was performed with Student's *t* test.

Results of Arterial Inflow Studies

Single nerve stimulation

Cavernous nerve. Intracorporeal pressure changes (ICP), arterial blood flow increase in the internal pudendal artery (IPA) and systemic blood pressure during cavernous nerve stimulation were monitored simultaneously (Table 1). After initiation of neurostimulation, the penis elongated slightly but engorged before it became tumescent up to a full erection. With a latency of 7 to 10 s after current was applied to the cavernous nerve, the baseline intracorporeal pressure of 25 cm H_2O rose to a mean peak pressure of 123.8 cm H_2O and stabilised (Table 2, Fig. 2A). The high pressure plateau was maintained as long as current was applied to the nerve bundle. The arterial inflow through the internal pudendal artery increased by more than 800% immediately after electrostimulation was initiated and started to decrease slowly as soon as full erection was achieved (Table 1, Fig. 2A). The

Table 1 Arterial Inflow Studies—Single Cavernous Nerve Stimulation

Intracorporeal pressure (ICP) (cm H_2O) ±SD			*Flow in internal pudendal artery (ml/min) ±SD*	
Base	*Peak*	*Rise*	*Base*	*Peak*
25 ±8.68	123.8* ±37.59	98.8 ±33.2	4.8 ±3.1	44.1† ±23.8

Each of the 6 dogs was tested twice. Mean values ±SD (= Standard Deviation)

* $P < 0.005$

† $P < 0.005$.

Table 2 Arterial Inflow Studies—Single Hypogastric Nerve Stimulation

Intracorporeal pressure (ICP) (cm H_2O) ± SD			*Flow in internal pudendal artery (ml/min) ± SD*	
Base	*Peak*	*Rise*	*Base*	*Peak*
23.4 ±7.9	25.1* ±9.4	1.7 ±5.47	3.0 ±1.7	13.0† ±13.2

6 dogs were tested Mean values ±SD (=Standard Deviation)
* $P<0.44$.
† $P<0.071$.

systemic blood pressure remained stable (mean 162 cm H_2O) during the entire stimulation trial.

Hypogastric nerve. The erectile response under hypogastric nerve stimulation differed from cavernous nerve activation. No engorgement or elongation of the penile shaft was observed, and the intracorporeal pressure did not change significantly ($P=0.44$). The arterial flow to the penis (IPA) increased by 333% (Table 2, Fig. 2B) 3 to 5 s after the current was applied to the hypogastric nerve fibres. After a delay of 5 to 7 s the systemic blood pressure rose to a mean value of 181 cm H_2O.

Combined cavernous and hypogastric nerve stimulation

Cavernous-hypogastric nerve. After initiation of cavernous nerve stimulation the intracorporeal pressure rose to an average of 127.5 cm H_2O until full erection was achieved and the arterial inflow increased by 851%. This was similar to the previous studies (Table 3, Fig, 3).

After 1 min of continuous cavernous nerve stimulation the sympathetic nerve fibres were also activated. Within 15 s (mean value) the intracorporeal pressure and systemic blood pressure changed significantly (Table 3, Fig. 3). Although neurostimulation of the cavernous nerve was maintained, detumescence occurred and the intracorporeal pressure declined significantly by 51% to a mean level of 62 cm H_2O ($P<0.005$). The systemic blood pressure increased to 177.5 cm H_2O ($P=0.001$) but the arterial inflow showed no significant change ($P=0.242$).

One minute after cessation of the additional sympathetic stimulation the intracorporeal pressure remained stable at a low pressure level for 15 to 28 s before rising again to an almost fully erect state (101 cm H_2O; $P=0.003$). At that point the blood pressure had already declined to its baseline level and the arterial inflow showed no significant change on continuation of cavernous nerve stimulation (Fig. 3).

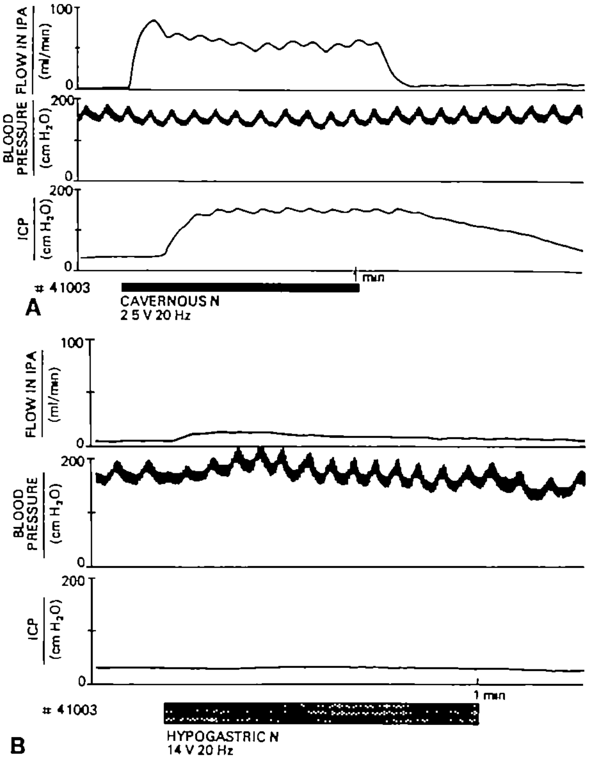

Fig. 2 (A) Internal pudendal artery flow (IPA), systemic blood pressure and intracorporeal pressure (ICP) were measured during erection induced by stimulation of the cavernous nerve (B) Stimulation of the hypogastric nerve did not produce erection. Note the changes in IPA flow and in systemic blood pressure

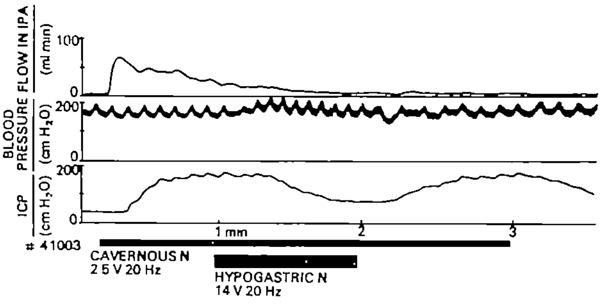

Fig. 3 Typical erectile response to cavernous stimulation. Additional excitation of the hypogastric nerves caused detumescence (intracorporeal pressure drop, ICP) and rise in systemic blood pressure but no significant change in arterial inflow (IPA) With continuation of the cavernous nerve stimulation, erection recurred

Hypogastric-cavernous nerve. In a second trial of combined sympathetic and cavernous nerve stimulation the hypogastric nerve was stimulated prior to the cavernous nerve. As described above, hypogastric nerve stimulation alone did not induce erection or any significant change in intracorporeal pressure (Table 4). However, the arterial inflow through the internal pudendal artery and the systemic blood pressure showed a moderate to strong increase.

With additional stimulation of the cavernous nerve bundle the intracorporeal pressure rose slowly to a mean peak pressure level of 99.2 cm H_2O before declining to a mean pressure plateau of 73.6 cm H_2O (Table 4). In no case could a full erection be maintained. In 1 dog even the moderate erection diminished and full detumescence occurred immediately after peak intracorporeal pressure was achieved. The arterial flow increased by only 370% and the systemic blood pressure remained stable, having previously declined to baseline level.

Continued cavernous nerve stimulation alone did not alter any of the parameters significantly. The intracorporeal pressure increased only slightly by 21.2 cm H_2O ($P=0.326$).

Table 3 Arterial Inflow Studies—Combined Cavernous and Hypogastric Nerve Stimulation

Stimulation Mode	*Intracorporeal pressure (ICP) (cm H_2O) ±SD* Base	Peak	*Systemic blood pressure (cm H_2O) ±SD*	*Flow in IPA (ml/min) ±SD* Base	Peak
Cavernous N	23.7 ±8.5	127.5* ±37.5	164.2† ±17.3	4.3 ±2.6	40.4 ±20.2
Cavernous and Hypogastric N	122.8 ±37.3	62.1*§ ±36.3	177.5† ±17.1	9.6‡ ±5.4	14.1‡ ±11.7
Cavernous N continuation	62.1 ±36.3	100.7§ ±58.9	165.0 ±18.8	8.8‖ ±6.8	7.2‖ ±3.6

6 dogs were tested Mean values ±SD (=Standard Deviation)
* $P<0.005$; ICP peak pressures
† $P=0.001$, systemic blood pressures.
‡ $P=0.242$, IPA flow change
§ $P=0.003$, ICP peak pressures (cont)
‖ $P=0.495$, IPA flow change (cont)

Table 4 Arterial Inflow Studies—Combined Hypogastric and Cavernous Nerve Stimulation

Stimulation Mode	*Intracorporeal pressure (ICP) (cm H_2O) ±SD* Base	Peak	*Systemic blood pressure (cm H_2O) ±SD*	*Flow in IPA (ml/min) ±SD* Base	Peak
Hypogastric N	21.2 ±8.0	21.6* ±8.2	192.0† ±25.9	2.2 ±1.8	12.5 ±15.9
Hypogastric # and Cavernous N	21.6 ±8.2	99.2*§ ±34.8	182.0† ±21.7	5.0‡ ±5.4	23.7‡ ±20.5
Cavernous N continuation	73.6 ±23.8	94.8§ ±45.6	178.0 ±21.7	5.7‖ ±5.9	4.3‖ ±3.2

4 dogs were tested Mean values ±SD (=Standard Deviation)
# In 1 dog full detumescence occurred after the ICP had passed its peak level In all dogs studied erection could not be maintained
* $P=0.004$, ICP peak pressures
† $P=0.09$, systemic blood pressures
‡ $P=0.056$, IPA flow change
§ $P=0.86$, ICP peak pressures (cont)
‖ $P=0.65$, IPA flow change (cont)

Results of Venous Outflow Studies

Single nerve stimulation

All 6 dogs underwent study of the venous outflow system with and without cavernous nerve stimulation. The baseline value was recorded during normal saline perfusion of the corpora cavernosa at a constant rate, with the aorta clamped temporarily. After the infusion was initiated, pressure rose to a mean peak level of 34.17 cm H_2O, at which point it stabilised or gradually dropped close to its baseline value (Table 5, Fig. 4).

Saline perfusion of the penis was continued for 1 min before electrostimulation of the cavernous nerve was applied. After an initial intracorporeal pressure drop under neurostimulation, indicating relaxation of the smooth muscles in the corpus cavernosum (Lue *et al.*, 1983a, 1987), pressure increased significantly ($P < 0.005$) within 104 s to a mean value of 193.33 cm H_2O. The peak values may be even higher because the pressure recording needle went off scale when 210 cm H_2O had been reached. This baseline study was consistent with our previous results showing that venous restriction occurred with neurostimulation-induced erection due to active intracorporeal smooth muscle relaxation (Jünemann *et al.*, 1986b, 1987a; Lue *et al.*, 1987).

Table 5 Venous Outflow Studies—Single Cavernous Nerve Stimulation

Perfusion/Stimulation Mode	*Intracorporeal pressure (ICP) (cm H_2O) ± SD)*	
	Base	*Peak*
Saline Perfusion (1.0–7.0 ml/min)*	20.7† ±6.4	34.2†§, ±76.1
Cavernous N.	33.3‡ ±12.9	193.3‡§ ±40.8

6 dogs were studied. Mean values ± SD (= Standard Deviation)

* Perfusion rate was dependent on size of penis (threshold parameters)

† $P = 0.014$, ICP change during saline perfusion.

‡ $P < 0.005$, ICP change during stimulation.

§ $P < 0.005$; ICP peak pressure changes.

Combined cavernous and sympathetic nerve stimulation

A rest period of 10 to 15 min was allowed before beginning the combined cavernous/hypogastric stimulation trial. First, baseline readings for saline perfusion without neurostimulation were performed (see above).

The same voltage as used before was applied to the cavernous nerve. As soon as the intracorporeal pressure had reached an average of 70.67 cm H_2O, additional hypogastric nerve stimulation was initiated (Fig. 5). With this combined stimulation a mean intracorporeal peak pressure level of 127.67 cm H_2O was achieved, only to decline to 62.2 cm H_2O within 31.17 s (mean) after hypogastric stimulation was initiated (Table 6, Fig. 5). In none of the dogs studied could the pressure peak be maintained and erection subsided, indicating blockage of the venous restricting mechanism.

Continuation of cavernous stimulation after hypogastric nerve stimulation was finished resulted in a renewed intracorporeal pressure increase by almost 60% (up to 95.7 cm H_2O) within 20 to 30 s. In 2 dogs the second pressure rise was not significant; in 1 dog it went off scale (>210 cm H_2O).

Discussion

The experimental studies were designed not only to show the effects of single and combined stimulation of various nerves which are involved in the erectile mechanism, but also to explain their interaction. The arterial inflow studies with cavernous nerve stimulation alone were consistent with the results

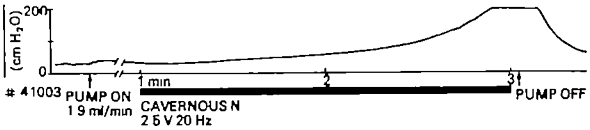

Fig. 4 Aorta clamped intracorporeal saline perfusion produced slight elevation of baseline pressure in the corpus cavernosum. Full erection developed with cavernous nerve stimulation (ICP far above systemic blood pressure).

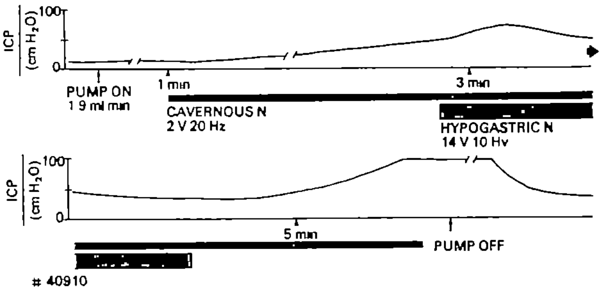

Fig. 5 Same dog as before. With additional hypogastric nerve stimulation venous outflow restriction due to sinusoidal relaxation (cavernous nerve stimulation) is blocked, leading to a decline in intracorporeal pressure. Termination of sympathetic stimulation and continuation of cavernous nerve stimulation resulted in a full erection

Table 6 Venous Outflow Studies—Combined Cavernous and Hypogastric Nerve Stimulation

Perfusion/Stimulation Mode	*Intracorporeal pressure (ICP) (cm H_2O) ±SD*	
	Base	*Peak*
Saline Perfusion (1.0–7.0 ml/min)*	21.7 ±5.9	33.5† ±12.6
Cavernous N.	32.0 ±12.5	127.7†‡ ±46.5
Cavernous and Hypogastric N‖	127.7‡ ±46.5	60.2‡§ ±26.8
Cavernous N continuation	60.2§ ±26.8	95.7§ ±63.1

6 dogs were tested. Mean values ±SD (=Standard Deviation).

* Perfusion rate was dependent on size of penis (threshold parameters).

‖ Peak pressure could not be maintained and erection subsided in all dogs.

† $P=0.006$, ICP change saline perfusion vs cavernous stimulation.

‡ $P=0.038$, ICP change cavernous vs combined stimulation.

§ $P<0.09$, ICP change combined vs cont. cavernous stimulation.

from previous studies indicating that initiation and maintenance of erection is under parasympathetic control (Lue *et al.*, 1983a; Jünemann *et al.*, 1987b). Stimulation of the cavernous nerve bundle resulted in full erection without complete rigidity. Stimulation of the upper hypogastric nerve alone, however, did not induce any significant intracorporeal pressure change or visible enlargement of the penile shaft. The interpretation of the sympathetic effect on systemic blood pressure and arterial blood flow (flow measured through the internal pudendal artery) to the penis was somewhat controversial. Sympathetic excitation results in increased blood pressure and penile vasoconstriction (Semans and Langworthy, 1938; Klinge and Sjøstrand, 1977). The latter effect should lead to a decrease in the arterial flow into the corpora cavernosa. In our study, however, sympathetic nerve stimulation resulted in an increased inflow above 300%. Since the arterial flow change was up to 4 s prior to the increase in blood pressure it is unlikely that this phenomenon is due to the systemic blood pressure increase. In our opinion, it is probably the result of a partial stimulation of parasympathetic fibres, the nervi erigentes, which join the hypogastric plexus (Semans and Langworthy, 1938; Root and Bard, 1947). This is consistent with the findings of Dail *et al.* (1985), who reported that the hypogastric nerve contains 20% preganglionic penile neurones. However, the nature of the neurotransmitters involved in the hypogastric pathway is unknown. They concluded that these nerve fibres were not necessarily sympathetic and may represent an alternative vasodilator system supplying the erectile tissue.

The most interesting findings in our study were produced with combined neurostimulation. Once the erection induced by stimulation of the cavernous nerve stabilised and remained at a high intracorporeal pressure level, additional hypogastric nerve stimulation resulted in subsidence of erection and the intracorporeal pressure dropped significantly by more than 50%. Detumescence occurred within 15 s, indicating that this phenomenon was due to a direct sympathetic effect on the erectile tissue. The significant pressure rise and the recurrence of erection under continuous cavernous stimulation after the sympathetic excitation was completed proved that detumescence and suppression of penile erection were under sympathetic control. Similar findings were made when the hypogastric nerve was stimulated prior to the cavernous nerve. The maximum peak pressure with combined neurostimulation was below the control results with cavernous stimulation alone, and a full erection could not be maintained once the intracorporeal pressure peak was reached. The effect of increased sympathetic excitation on the erectile response, however, cannot be due to reduced arterial inflow alone. The rapid detumescence and the failure to maintain an already achieved erection indicate that the haemodynamic effect of hypogastric nerve stimulation must have taken place on the venous outflow system of the corpora cavernosa.

This conclusion is supported by the results of the venous outflow studies. Single cavernous nerve stimulation of a saline-perfused canine penis resulted in venous outflow restriction and, subsequently, in full erection due to smooth muscle relaxation of the corporeal tissue (Lue *et al.*, 1984a; Jünemann *et al.*, 1986b, 1987a). Repetition, after sufficient recovery time, with the same stimulation parameters plus additional hypogastric nerve stimulation blocked the venous outflow restriction mechanism. In all dogs studied detumescence occurred within 30 s after hypogastric stimulation was initiated, indicating that the increased sympathetic excitation caused a contraction of the smooth muscles in the corpus cavernosum, leading to a venous leak. The recovery of this system with continuation of cavernous stimulation alone showed that the blocking effect of venous outflow restriction was under sympathetic control. We postulate that detumescence is more likely to be an active mechanism rather than a purely passive phenomenon as proposed by Lue *et al.* (1983a, 1984a).

These findings are of importance since clinical data have shown that up to 20% of patients with erectile dysfunction are diagnosed as having "venous leakage" or "cavernous insufficiency" (Jünemann *et al.*, 1988). This often leads to invasive operative treatment, although the success rate remains unsatisfactory. Recognition of a high sympathetic output might provide a therapeutic option. Furthermore, the exact role of the sympathetic nervous system in psychogenic impotence requires clarification.

Our *in vivo* studies have shown that:

1. Hypogastric nerve stimulation can subside or suppress penile erection.
2. The major effect of hypogastric excitation is on the erectile tissue itself by blocking the venous outflow restriction depending on cavernous smooth muscle relaxation.
3. A high sympathetic output may induce venous leakage or cavernous insufficiency.
4. Detumescence is a sympathetic phenomenon.

Studies on the neurological aspects of the initiation and maintenance of penile erection (Jünemann *et al.*, 1987b), together with our newly acquired appreciation of the mechanism for subsidence of erection and detumescence, have increased our understanding of the neurophysiological mechanisms of penile erection. Cavernous nerve excitation causes sinusoidal relaxation and maximum arterial dilatation, culminating in a marked increase in arterial inflow (Leu *et al.*, 1983a; Jünemann *et al.*, 1987a). The functional state of the penis changes from flaccid to latent and, subsequently, with the increase of intracavernous blood volume and complete corporeal smooth muscle relaxation, venous restriction occurs, producing turgidity of the corpora cavernosa and the corpus spongiosum (tumescence phase). In a fully erect state the intracorporeal pressure is 10 to 30 cm H_2O below systemic blood pressure. These 4 phases of penile erection and predominantly under parasympathetic control (cavernous nerve bundle) and have to be understood as the "vascular mechanism" of erection (Jünemann *et al.*, 1987b). Subsequent contraction of the bulbocavernosus and ischiocavernosus muscles compresses the blood-distended proximal corpora and results in cavernosal rigidity and further engorgement of the glans penis (rigidity phase). The intracavernous pressure rises well above systemic blood pressure. These muscles are controlled by somatotopic nerve fibres deriving from the pudendal nerve. The mechanism of penile rigidity is defined as the "muscular mechanism" of erection. Finally, with stimulation of the sympathetic nervous system, smooth muscle constriction of the erectile tissue and retraction of the corpora cavernosa result in subsidence of erection (detumescence phase). The sympathetic effect implies 2 mechanisms in penile erection: the detumescence controlling part in the physiological erectile mechanism and a blocking effect on corporeal smooth muscle relaxation, resulting in cavernous insufficiency. This phenomenon should be understood as the "inhibitory mechanism" of penile erection.

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Intra-individual Comparative Study of Dynamic and Pharmacocavernography

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Summary—A series of 65 consecutive patients with suspected venous leakage as a cause of their erectile dysfunction underwent dynamic and pharmacocavernometry/cavernography. This comparison of methods for diagnosing venous leakage produced divergent findings in 25/65 patients (38.5%). Because of its theoretical advantages, pharmacocavernometry/cavernography is recommended for the diagnosis of venous leakage.

Newman *et al.* (1964) were the first to describe the phenomenon of passive erection by perfusion of the cavernous bodies or the internal iliac artery. Virag *et al.* (1979) induced artificial erection by saline perfusion of the cavernous bodies in the diagnosis of erectile dysfunction. The lowest rate of saline perfusion required to maintain full erection was known as maintenance flow (cavernometry). In full erection, the penis was then perfused to opacify the abnormally draining veins (cavernography).

Lue *et al.* (1984) and Juenemann *et al.* (1985) showed that the cavernous haemodynamic changes which follow direct neurostimulation are similar to those following the intracavernous injection of vasoactive drugs. It was therefore suggested that cavernometry/cavernography should be done after pharmacologically induced cavernous relaxation (Lue *et al.*, 1986). The purpose of this study was to establish possible differences in the diagnostic information provided by dynamic and pharmacocavernometry/cavernography.

Patients and Methods

In all patients attending our impotence clinic the following investigations were done: a detailed history was taken with the aid of a questionnaire, with the emphasis on sex life, possible risk factors and situation-related erection processes and libido. Physical and neurological examination, SMA 12 including testosterone and prolactin and nocturnal penile tumescence (NPT) measurements by means of a Jonas snap-gauge were followed by Doppler studies of both dorsal and cavernous penile arteries, proximally and distally, after the intracavernous injection of vasoactive drugs (Jevtich, 1984). Standardised intracavernous injections of a combination of papaverine and phentolamine were then given (Stief *et al.*, 1988).

Venous leakage was suspected if the patient did not respond with a full erection to maximum doses of vasoactive drugs (45 mg papaverine and 1.5 mg phentolamine) or if he showed intact penile arterialisation in Doppler studies (good blood flow in at least one cavernous and dorsal penile artery (Gall *et al.*, 1988)) after the intracavernous injection of vasoactive drugs and a poor erectile dysfunction was also an indication for cavernometry/cavernography, since previous studies showed that almost half of these patients had venous leakage.

In 65 consecutive impotent patients with suspected venous leakage, dynamic and pharmacocavernometry/cavernography were performed one after the other in the same patient. Under sterile conditions, the right proximal cavernous body was punctured without local anaesthesia for perfusion with a 19 gauge butterfly cannula. A Fresenuis perfusion pump mixed a maximal perfusion rate of 400 ml/min (model BP 742, Fresenius AG, Bad Homburg, FRG) was used for flow rates from 40 to 300 ml/min. For flow rates lower than 40 ml/min the perfusion was done by a urologist with a 60-ml syringe because it is more accurate than the pump in this flow range. A 26 gauge needle was inserted

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into the contralateral cavernous body for intracavernous pressure recording.

For dynamic cavernography, 0.9% saline (37°C) was perfused at a rate of 300 ml/min to induce a full erection (80 mm Hg). If a full erection was not induced within 90 s we proceeded directly to contrast medium (Ultravist 300, Schering AG, Bergkamen, FRG; Solutrast, 300, Byk Gulden, Konstanz, FRG) perfusion to avoid circulatory problems. After measuring the maintenance flow (mf 1) and following opacification of the cavernous drainage, 30 mg papaverine and 1 mg phentolamine were injected intracavernously; 10 min later, measurement of the maintenance flow (mf 2) and opacification of the cavernous drainage were repeated (pharmacocavernometry/cavernography).

To prevent possible endothelial changes caused by the hyperoncotic contrast medium, the penis was perfused with 30 to 50 ml saline. To prevent intradermal or subcutaneous haematomas after the needles were removed, the puncture sites were compressed manually for at least 5 min.

As a control group, 14 patients with congenital penile deviation underwent dynamic cavernometry/cavernography. A further 8 patients with congenital penile deviation underwent pharmacocavernometry/cavernography.

Results

In the control group for dynamic cavernometry, the maintenance flow was 18 to 65 ml/min (mean 41). For pharmacocavernometry, the maintenance flow in the control group was 4 to 14 ml/min (mean 7). Only slight cavernosal drainage (or none at all) was seen during contrast medium perfusion in both groups (Fig. 1).

Primary erectile dysfunction was noted in 17/65 patients: 6 had insulin-dependent diabetes; impotence was related to a pelvic fracture in 4 patients and 3 had had Peyronie's disease for at least 1 year; in 1 patient, impotence developed after iatrogenic sphincterotomy during TUR of the prostate. No patient had hormonal abnormalities. Investigations revealed concomitant arterial disease in 21/65 patients. Neurological abnormalities were suspected in 5 and concomitant psychogenic abnormalities in 3.

The maintenance flow in dynamic cavernometry was 35 to 275 ml/min (mean 103) in 41 patients. The induction flow (300 ml/min) failed to induce full rigidity in 24 patients. In pharmacocavernometry the maintenance flow was 3 to 220 ml/min (mean 55) in 63 patients. Full rigidity could not be induced in 2 cases.

When the patients were divided into 2 groups, 1 achieving full rigidity in dynamic cavernometry and the other failing to do so, it was found that those who did not attain full rigidity (mf 1 > 300 ml/min) had a markedly higher mf 2 (22 patients 5–220 ml/min, mean 112 ± 89; 2 patients > 300 ml/min) than those achieving full rigidity (mf 3–220 ml/min, mean 45 ± 33). This difference was statistically significant (Student's *t* test; $P = 0.001$).

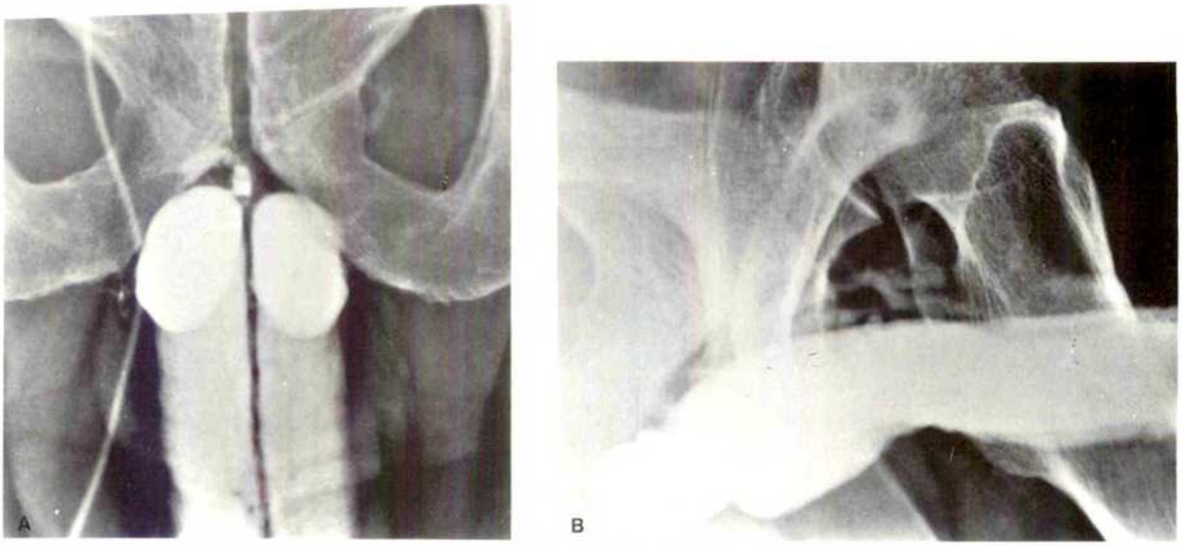

Fig. 1 Normal cavernography. No drainage or only slight cavernosal drainage is visible. (A) anterio-posterior. (B) oblique.

Eight patients had abnormal dynamic cavernometry and normal pharmacocavernometry with corresponding cavernography (Fig. 2). In 3 patients, dynamic cavernometry/cavernography was normal, but pharmacocavernometry/cavernography was abnormal. In 11/65 patients with abnormal cavernous drainage via superficial and deep dorsal penile veins in dynamic cavernography, pharmacocavernography revealed the drainage to be via the superficial vein(s) to the saphenous vein(s) (Fig. 3); 3/10 patients with abnormal drainage via deep dorsal and cavernous veins in dynamic cavernography did not show cavernous veins in pharmacocavernography.

In 40/65 patients, identical findings were noted in dynamic and pharmacocavernometry/cavernography: 32 had venous leakage and 8 had normal cavernous drainage. In 4 patients, abnormal cavernous drainage was via a superficial penile vein to the cavernous vein. (Fig. 4).

Apart from 12 small ecchymoses on the site of the 19 gauge needle, we saw 2 cases of extensive subcutaneous oedema. One occurred during saline perfusion and was resorbed within hours. The other occurred during contrast medium perfusion and caused continuous penile shaft swelling due to the hyperoncotic contrast medium. This was also resorbed without therapy within 2 days. One patient reported dizziness on cavernography; 2 complained of intrapenile pain during saline perfusion, which could not be treated by changing the position of the butterfly cannula. There was no subcutaneous infection or cavernitis.

Discussion

The maintenance flow established for dynamic cavernometry in the control group confirms the findings of other investigators (Porst *et al.*, 1987). The parameters for pharmacocavernometry are similar to those for psychogenic-impotent patients (Wespes *et al.*, 1986).

Five of 8 patients in the control group for pharmacocavernometry did not have full erections at the end of pharmacocavernometry/cavernography despite an adequate dose of vasoactive drugs. We attribute this to the elevated intracavernous adrenergic tonus (Buvat *et al.*, 1986) and to a washout effect by the saline perfusion. To prevent a prolonged erection in 3/8 patients with remaining high intracavernous pressures (over 80 mm Hg) over 10 min after the end of the procedure, 2 mg metaraminol were injected intracavernously (Brindley, 1984).

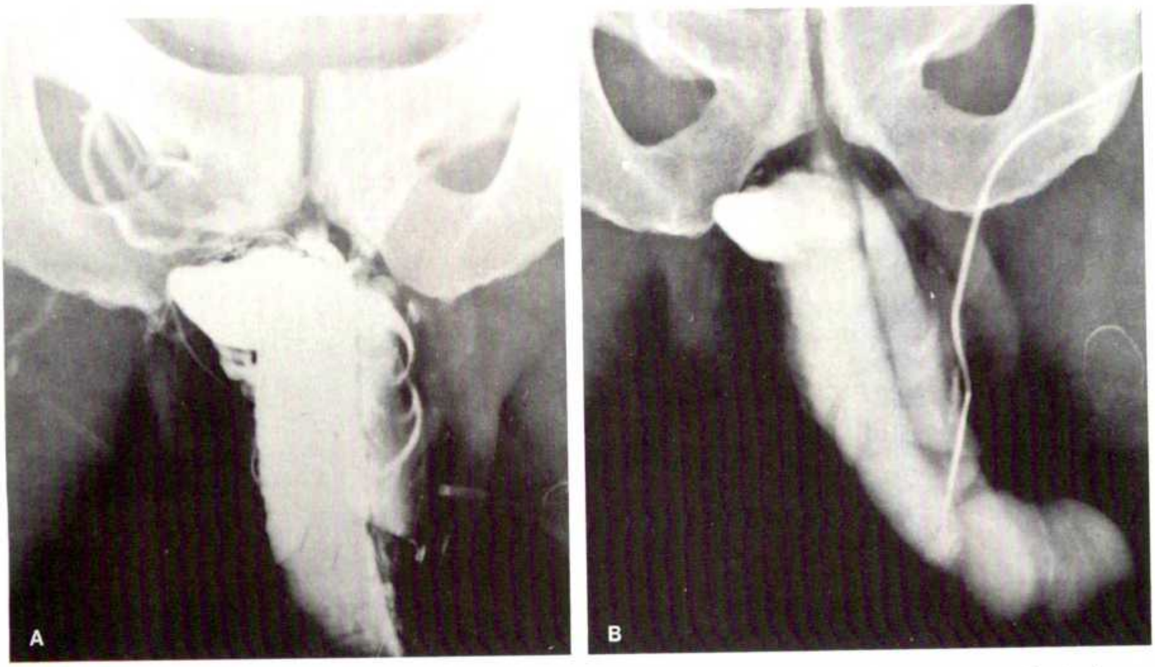

Fig. 2 (A) Dynamic cavernography with abnormal drainage via the dorsum penis. (B) Pharmacocavernography in the same patient shows normal findings.

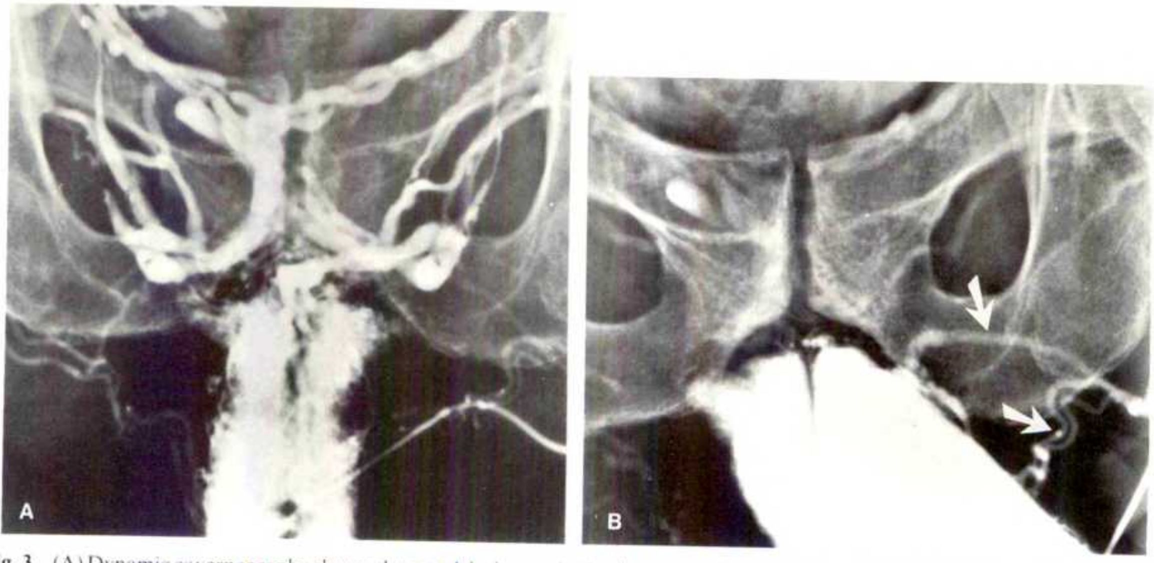

Fig. 3 (A) Dynamic cavernography shows abnormal drainage via the dorsum penis and ectopic veins. (B) Pharmacocavernography in the same patient shows the abnormal drainage only via ectopic veins (arrows).

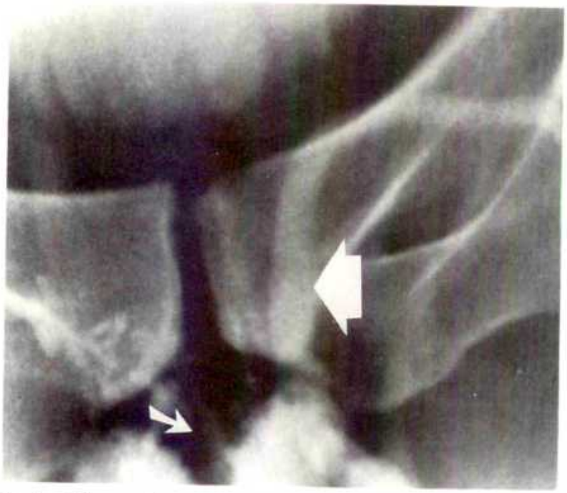

Fig. 4 Abnormal cavernous drainage via an ectopic vein (large arrow); there is no drainage via the deep dorsal penile vein (small arrow).

The venous occlusive mechanism for penile erection consists of at least 2 phenomena: firstly, the emissary veins, running obliquely through the tunica albuginea, are squeezed during tumescence (Lierse, 1982); secondly, the venular plexus interposed between the tunica albuginea and the sinusoidal spaces is compressed following relaxation of the cavernous smooth muscles (Fournier *et al.*, 1987). Saline perfusion of the cavernous bodies seems to imitate only the first part of the venous occlusive mechanism, whereas saline perfusion after cavernous smooth muscle relaxation seems to imitate both parts. These different targets could explain the different intra-individual findings: 25/65 consecutive patients (38.5%) showed different results in dynamic and pharmacocavernometry/cavernography respectively. This is of decisive importance because cavernometric and cavernographic findings are a major contribution to the indications for venous surgery.

Our comparative study shows that the results of dynamic cavernometry/cavernography cannot be compared with those of pharmacocavernometry/cavernography in all patients. The latter procedure should be used because of the theoretical advantages in imitating the physiological erection. This must be corroborated by further experimental studies and long-term results of venous leak surgery. In addition, it offers practical advantages such as savings in saline and contrast medium solution.

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Case Reports

Late Presentation of Congenital Posterior Urethral Valves

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Bladder outflow obstruction caused by congenital posterior urethral valves is a well defined surgical condition which presents in early life. Presentation after the age of 10 years is rare.

Case Report

A 13-year-old West Indian boy presented with acute urinary retention, preceded by a 4-week history of a deteriorating urinary stream, frequency, straining and nocturnal enuresis. There was no significant past medical history apart from circumcision for a phimosis aged 2 years. On examination the bladder was distended and tender; there were no neurological abnormalities. Haemoglobin, midstream urine, blood urea and electrolyte levels were all normal. Plain abdominal X-ray revealed spina bifida occulta of the lower sacrum. Ultrasound scan demonstrated bilateral hydronephrosis and ureters dilated down to the bladder, which was thick-walled with a moderate residual urine. Intravenous urography confirmed these changes of outflow obstruction (Fig.) and posterior urethral valves were identified on voiding. At urethroscopy 2 mucosal ridges were identified running from the verumontanum to the bladder neck and these were divided; 6 months post-operatively he had a good urinary stream with a flow rate of 18 ml/s and 2 years later he remains well with a normal urinary stream.

Comment

Congenital posterior urethral valves present early (22% at birth and 52% in the first 3 months of life (Scott, 1985)); 72% of these children have renal failure at the time of diagnosis. Younger children usually present with obstruction and have a greater degree of renal impairment than older children, who tend to present with infective problems. Our patient presented late with acute urinary retention and gross dilatation of the urinary tract but with normal serum creatinine and urea levels. This is an unusual presentation even in the adult (Marsden, 1969).

Although treatment effectively relieves outflow obstruction, patients may have problems later because of a poorly compliant bladder.

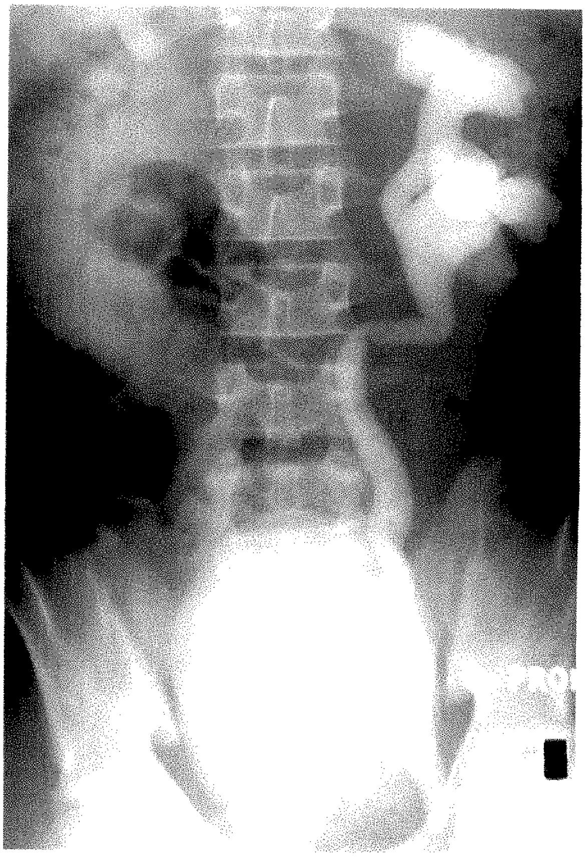

Fig. Intravenous urogram showing bilateral hydronephrosis and ureteric dilatation.

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Renovascular Hypertension Associated with Narrowing of the Infrarenal Aorta

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Case Report

A 17-year-old woman had a retroperitoneal teratoma resected at age 4 months and a patent ductus arteriosus closed at age 7 years, when hypertension had been noted. Antihypertensive medication proved ineffective. The plasma renin activity was elevated (14.7 ng/ml/h). Transaxillary aortography disclosed that the infrarenal aorta was narrowed and became the rectal artery without bifurcating into the common iliac arteries (Figs 1 and 2). The right renal artery was not visualised. The lower intercostal and subcostal arteries served as collateral pathways to the femoral arteries. Cavography did not reveal an inferior vena cava but showed dilated paravertebral veins.

The right kidney (weighing 45 g) was removed. It had 3 renal arteries 1 mm in diameter. Histologically, the renal parenchyma was normal except for thickened arterioles. The renal arteries were also normal except for focal protrusion of the media into the lumen. Postoperatively the blood pressure and plasma renin activity returned to normal.

Comment

This patient had renovascular hypertension with a rare cause. The aortogram and histology of the involved renal arteries were inconsistent with fibromuscular dysplasia, arteriosclerosis or Takayasu's arteritis (Bron, 1966; Kirshbaum, 1970). Aortic disease probably led to stenosis of the right renal arteries, which arose from the narrow aorta. The previous excision of a retroperitoneal teratoma may have caused this aortic anomaly and occluded the inferior vena cava, although maldevelopment is an alternative explanation.

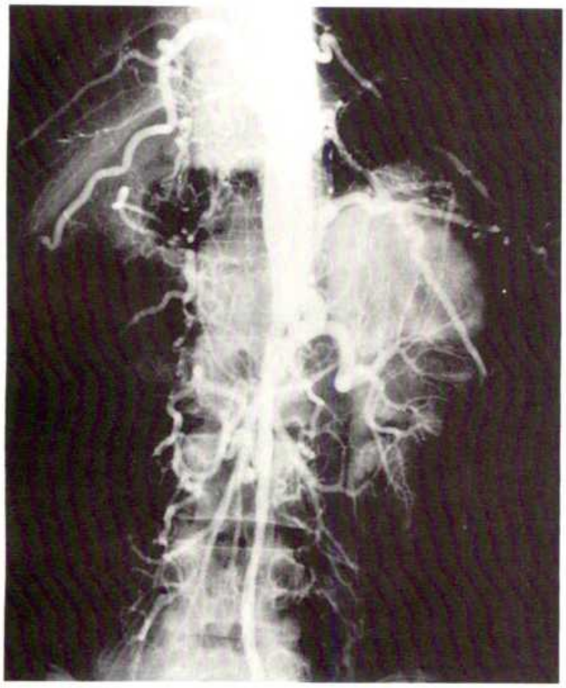

Fig. 1 Transaxillary aortography. Infrarenal aorta is narrowed over its entire length. Right renal artery is not visualised.

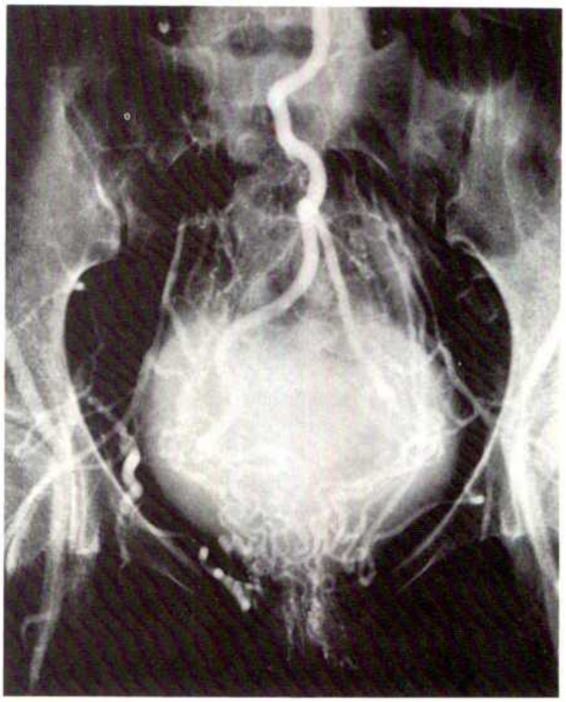

Fig. 2 Narrow aorta is transformed into rectal artery without bifurcating into common iliac arteries. Dilated deep circumflex iliac arteries constitute collateral pathways.

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Requests for reprints to: A. Ogawa, Department of Urology, Shinshu University School of Medicine, 3-1-1 Asahi, Matsumoto, 390 Japan.

Nephrogenic Caliceal Adenoma

G. F. PRATI, A. MUOLO and P. DEAN, *Division of Surgical Nephrology, Verona Hospital, Verona, Italy*

Case Report

T.E., an 18-year-old female, had an episode of right renal colic 16 months before admission to this department.

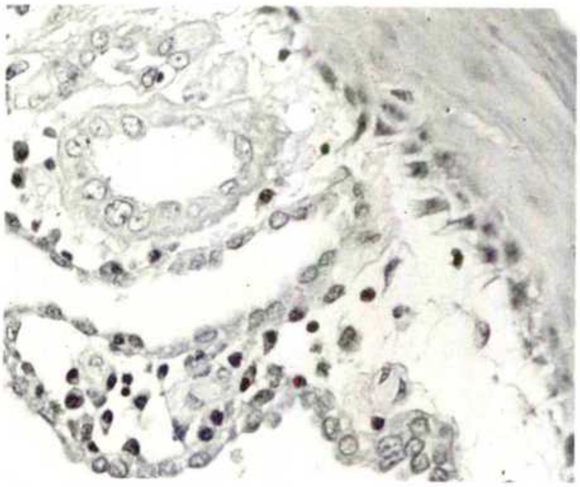

Fig. Below the metaplastic epithelium there is evidence of epithelial proliferation consisting of tubules and papillae covered by epithelial cells resting on the basement membrane. (PAS ×400).

Urography showed a calculus in a hydronephrotic right kidney.

Right pyelolithotomy and junctional ureteric debridement were performed at the patient's local hospital. Right renal colic recurred 4 months later. Urography showed an enormous hydronephrosis with severely impaired renal function and a right nephrectomy was performed. Histological examination confirmed hydronephrosis with chronic pyelonephritis and areas of transitional metaplasia of the caliceal epithelium, one calix containing a small nephrogenic adenoma (Fig.).

Comment

Nephrogenic adenoma, a proliferative benign lesion taking its name from its similarity in shape to Henle's loop and the distal tubules and collecting ducts, was thought for many years to occur only in the bladder. Its identification in urethral, ureteric (and now caliceal) tissue provides evidence that it can affect the whole of the urinary tract (Friedman and Kuhlenbeck, 1950; Mostofi, 1954).

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Friedman, N. B. and Kuhlenbeck, H. (1950). Adenomatoid tumors of the bladder reproducing renal structures (nephrogenic adenomas). *J. Urol.*, **64**, 657–660.

Mostofi, F. K. (1954). Potentialities of bladder epithelium. *J. Urol.*, **71**, 705–709.

Requests for reprints to: G. Prati, Via Farinati degli Uberti 8, I-37126 Verona, Italy.

Spontaneous Extravasation and Urinoma Formation Secondary to Cervical Carcinoma

S. McCLINTON, P. RICHMOND and J. H. STEYN,
Department of Urology, Royal Infirmary, Aberdeen

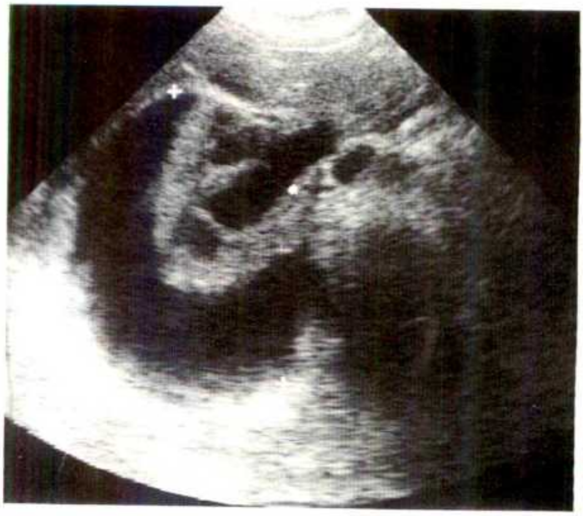
Case Report

A 28-year-old woman presented with a 2-month history of right-sided abdominal pain associated with frequency of micturition. On examination she was found to have a tender mass in the right loin. In 1977, as part of the investigations for recurrent urinary infections, she had intravenous urography and cystoscopy, which were normal. She was Para 2, with children aged 8 years and 16 months. She had defaulted from post-natal follow-up on both occasions.

Ultrasound scanning of the abdomen demonstrated a urinoma surrounding a grossly hydronephrotic right kidney (Fig.). The urinoma was so large that it was compressing and pushing the kidney medially to overlie the inferior vena cava. The upper ureter was also noted to be dilated.

The urinoma, containing 500 ml of blood-stained urine, was drained percutaneously by insertion of a 14 F Malecot catheter. At the same time a lower pole nephrostomy tube was inserted percutaneously. The urinoma drain was removed after 4 days, at which time an antegrade pyelogram was performed. This demonstrated no further extravasation from the kidney or ureter but did show an obstruction at the level of the vesicoureteric junction.

She then underwent cystoscopy and examination under anaesthesia. The bladder was normal but on examination under anaesthesia she was found to have an irregular cervix with a mass extending to the right pelvic wall.



Biopsy showed this to be a poorly differentiated squamous carcinoma of the cervix uteri (Stage IIIb).

Comment

Spontaneous extravasation of urine is usually due to acute obstruction secondary to a ureteric calculus (Cooke and Bartucz, 1974). However, the formation of a urinoma is usually associated with chronic ureteric obstruction and should suggest the possibility of tumour obstruction of the ureter (Twersky *et al.*, 1976).

Uraemia secondary to ureteric obstruction is a well recognised consequence of cervical carcinoma, either as a result of primary spread or as a late result of radiotherapy. Spontaneous extravasation of urine and urinoma formation is a rare sequela and an unusual presentation of cervical carcinoma in a young woman and has not been reported previously.

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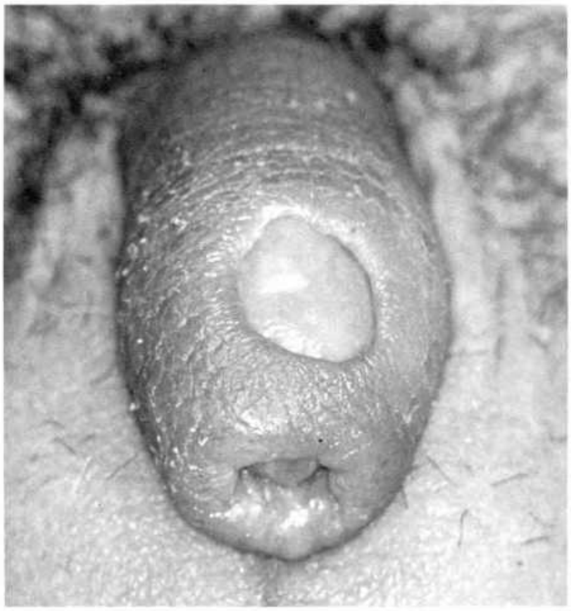
Requests for reprints to: S. McClinton, Department of Urology, Ward 44, Aberdeen Royal Infirmary, Foresterhill, Aberdeen AB9 2ZB.

Spontaneous Perforation of the Foreskin in Sweet's Syndrome

K. PAK, H. INOUE and T. TOMOYOSHI, *Department of Urology, Shiga University of Medical Science, Otsu, Japan*

Case Report

A 46-year-old man with phimosis, who had been treated with steroids for Sweet's syndrome, noticed a small ulcer on the dorsum of the penis in July 1987. During the next 2 months it developed into a circular defect of the foreskin, 1.5 cm in diameter (Fig.). The patient refused surgery because of his religious beliefs. In December 1987 another defect developed in the proximal foreskin and the 2 defects fused into a larger one through which the glans protruded. Dorsal incision was performed in February 1988. Histopathological examination failed to show the characteristic features of Sweet's syndrome.



Comment

The cardinal features of Sweet's syndrome are fever, neutrophil polymorphonuclear leucocytosis, raised painful plaques of the limbs, face and neck, and (histologically) a dense dermal infiltration with mature neutrophil polymorphonuclear leucocytes (Sweet, 1964). In the present case, histological examination did not reveal the characteristic features of Sweet's syndrome. It seems that balanoposthitis (in a patient with phimosis) together with steroid therapy led to perforation of the foreskin.

Reference

Sweet, R. D. (1964). An acute febrile neutrophilic dermatosis. *Br. J. Dermatol.*, **76**, 349–356.

Requests for reprints to: K. Pak, Department of Urology, Shiga University of Medical Science, Otsu, Shiga 520–21, Japan.

Haematuria Secondary to Idiopathic Renal Vein Varices

K. J. O'FLYNN and G. B. McKELVIE, *Department of Urology, Royal Infirmary, Stirling*

Case Report

An 18-year-old man presented with anaemia and haematuria. Intravenous urography showed no abnormality. At cystoscopy, blood was seen effluxing from the left

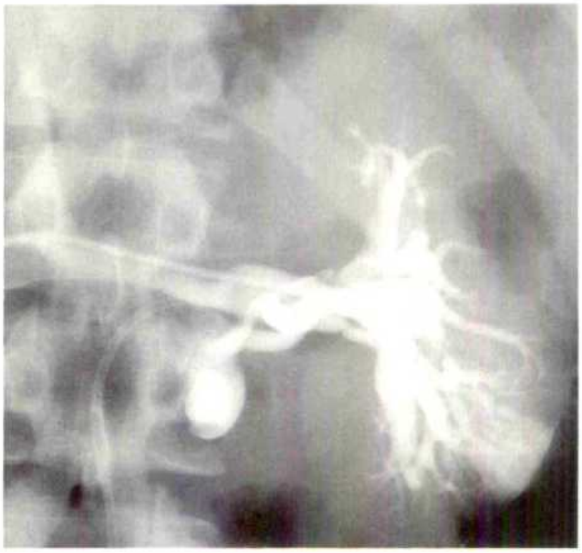


Fig. 1 Selective venogram reveals patency of renal vein and inferior vena cava.

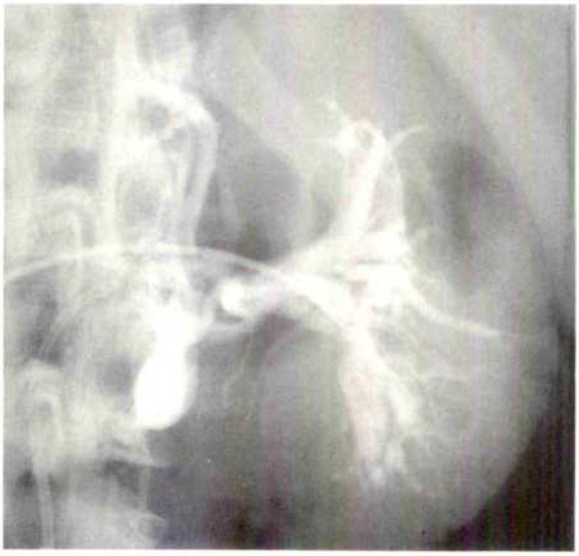


Fig. 2 Venogram shows varices communicating with vertebral venous plexus.

ureteric orifice. Retrograde pyelography was normal. Selective test renal arteriograms and adrenaline renal venography demonstrated patency of the left renal vein and an irregular complex of veins communicating with it (Fig. 1). The complex drained principally into the vertebral venous plexus (Fig. 2).

Exploration through a left flank incision revealed a large tortuous plexus of peripelvic veins which were carefully ligated. The patient made an uneventful recovery and 2 years later has had no further haematuria.

Comment

While renal vein varices are well documented following renal vein thrombosis and portal hypertension, there are few reports of idiopathic renal varices causing haematuria. Varices are probably more frequent than previously reported and in the majority of cases are asymptomatic (Beckmann and Abrams, 1982). Renal vein varices are commoner on the left side than the right, as are varicoceles, suggesting an anatomical abnormality (Blaivas *et al.*, 1977). Inherent weakness of the vein wall may play a role, as 30% have superficial varicosities.

Vascular studies are indicated in patients who have a persistent bloody efflux from one ureter and in whom intravenous urography and ultrasound are normal. Demonstration of the renal veins during arteriography is variable, depending on the presence or absence of renal disease and the amount of contrast material used. Visualisation of the renal bed is best obtained with deliberate slowing of the renal blood flow by injecting 10 μg adrenaline into the renal artery through a selectively placed arterial catheter while simultaneously injecting contrast material into the renal vein.

Thorough excision and ligation of the varicose veins is frequently curative and nephrectomy is indicated only for life-threatening haemorrhage. The role of sclerosing agents for obliterating renal vein varices has yet to be established (Cohen *et al.*, 1983).

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Blaivas, J. G., Previte, S. R. and Pais, V. M. (1977). Idiopathic pelvic ureteric varices. *Urology*, **9**, 207–211.

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Requests for reprints to: G. B. McKelvie, Department of Urology, Stirling Royal Infirmary, Livilands, Stirling FK8 2AU.

Obstruction of the Vena Cava Secondary to an Enlarged Bladder

H. S. MARKUS and J. T. O'BRIEN, *Department of Medicine, John Radcliffe Hospital, Oxford*

Inferior vena cava (IVC) obstruction may present with oedema of the lower half of the body. We present a case secondary to an enlarged bladder, in which the oedema rapidly resolved following catheterisation.

Case Report

A 70-year-old man was admitted with a 2-week history of swollen legs which had not responded to oral frusemide. He was not short of breath and denied urinary symptoms. On examination he had penile oedema and pitting oedema of both legs to the groins, but no other signs of cardiac failure. He had a non-tender bladder palpable to the umbilicus. Rectal examination revealed an enlarged prostate. Neurological examination was normal.

He was catheterised, and 3 l of urine were drained (Fig.). Ultrasound showed the IVC, which appeared patent. Despite stopping the frusemide on admission, he lost 8 kg over the next 10 days and the oedema resolved completely.

He subsequently underwent transurethral prostatectomy, followed by successful removal of the catheter. Histology was benign. Six months later he remains oedema-free and is not taking diuretics.

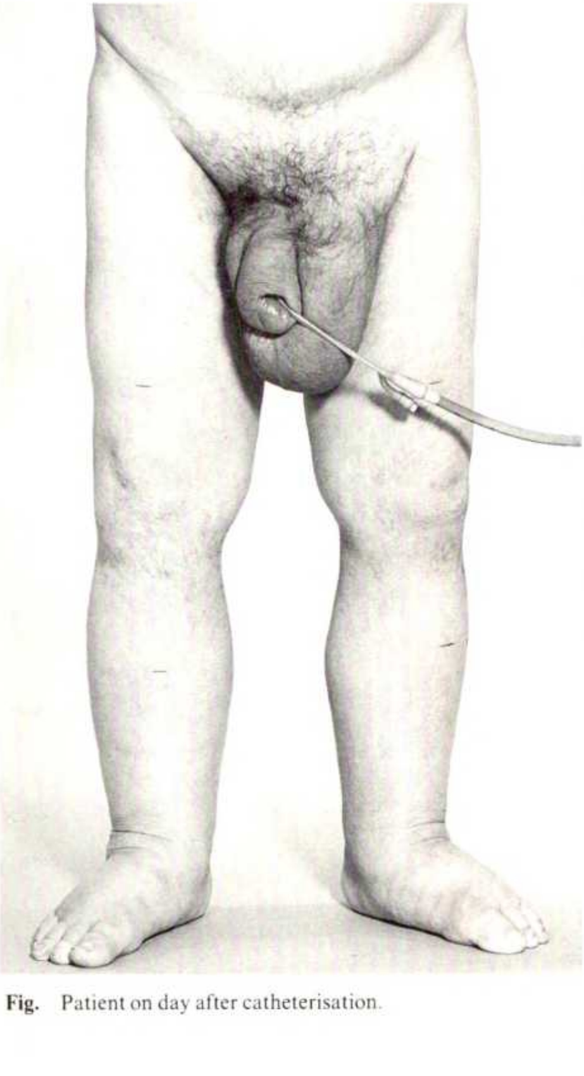

Fig. Patient on day after catheterisation.

Comment

It is likely that the enlarged bladder in our patient resulted in compression, and hence obstruction, of the IVC and/or the iliac veins. This is supported by the rapid resolution of, and long-term freedom from, oedema following relief of bladder outflow obstruction, and the patent IVC seen on ultrasound following catheterisation.

Many causes of IVC obstruction have been reported. Intrinsic lesions include renal carcinoma, thrombus and congenital membranes. Extrinsic lesions include neoplasia, retroperitoneal fibrosis, aortic aneurysms and the pregnant uterus (Kerr *et al*., 1964; Flye, 1983; Benbow, 1986). However, we can find no previous reports of a large bladder leading to IVC obstruction.

Acknowledgement

We thank Professor J. Grimley-Evans for permission to report this case.

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Requests for reprints to: H. S. Markus, Department of Medicine, University Hospital, Queen's Medical Centre, Nottingham NG7 2UH.

Renal Carcinoma Presenting as a Large Staghorn Stone

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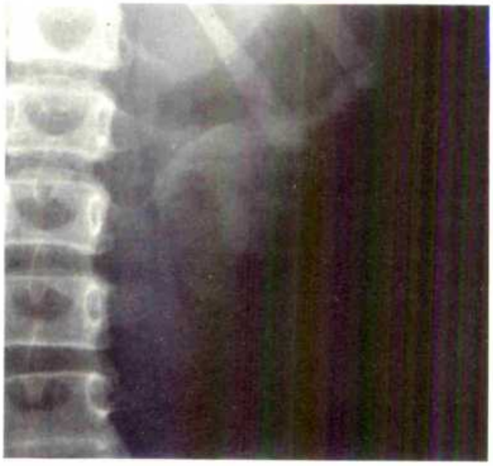
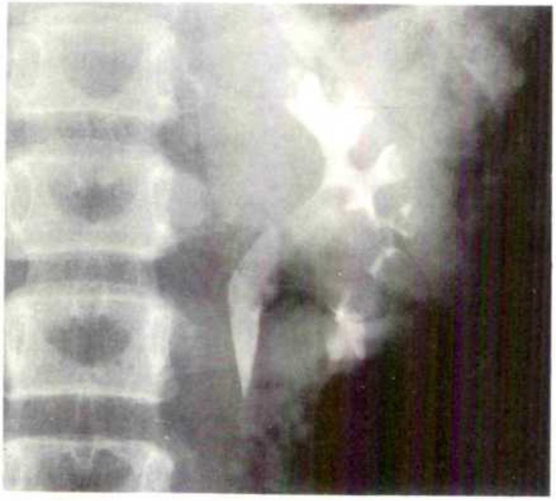
Departments of Urology, Radiology, Pathology and Pediatric Urology, Erasmus University Hospital Dijkzigt and Sophia Children's Hospital, Rotterdam, The Netherlands

Case Report

A 13-year-old white girl presented with a 1-year history of painless microhaematuria. There had been 2 short periods of macrohaematuria, also painless. There was no history of urinary tract infection, weight loss, temperature, loin pain, hypertension or stone passing, and there





was no family history of stone disease. Physical examination revealed no abnormalities. Urine pH was 5 and urine sediment showed many red blood cells. All other laboratory investigations were normal. An intravenous urogram showed faintly visible, staghorn, left-sided calcification on the plain X-ray (Figs 1 and 2). The patient was referred here for endourological and ESWL treatment.

A nephrostomy tube was inserted under ultrasonic guidance and general anaesthesia. (The radiologist did not notice the normal acoustic shadowing seen in large stones). After placing an Amplatz tube, a papillary tumour was seen. Frozen section showed a papillary epithelial malignancy with psammous bodies. Chest X-ray, CT scan and bone scan showed no abnormalities. A radical nephroureterectomy was performed. No abnormal lymph nodes were seen. On cut section a large tumour was seen occupying the renal pelvis, together with a circumscribed 1.5-cm tumour adjacent to the renal capsule in the cortex. Pathological examination revealed a renal carcinoma with local infiltration in the peripelvic tissue. Because of the likelihood of tumour spill, radiotherapy was given post-operatively to the renal area (44 Gray in 22 fractions with 19 MeV electrons).

The patient has been followed up for 20 months; she is doing well and is free of disease.

Comment

Renal carcinoma seldom appears in the first 2 decades of life but is perhaps less rare than is commonly assumed. Since 1934 more than 200 cases have been reported (Castellanos, 1974; Ruf, 1981 (unpublished material); Chan, 1983). Calcification in the tumour was found in 24% of cases, varying from a fine speckled appearance to a ring-like rim outlining the tumour. To our knowledge this is the first renal carcinoma with a staghorn appearance.

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Chan, H. S. L., Daneman, A., Gribbin, M. *et al.* (1983). Renal cell carcinoma in the first two decades of life. *Pediatr. Radiol.*, **13**, 324–328.

Requests for reprints to: M. T. W. T. Lock, University Hospital, St. Radboud, University of Nymegen, P.O. Box 9101, 6500 HB Nymegen, The Netherlands.

British Journal of Urology (1989), **64**, 105–106

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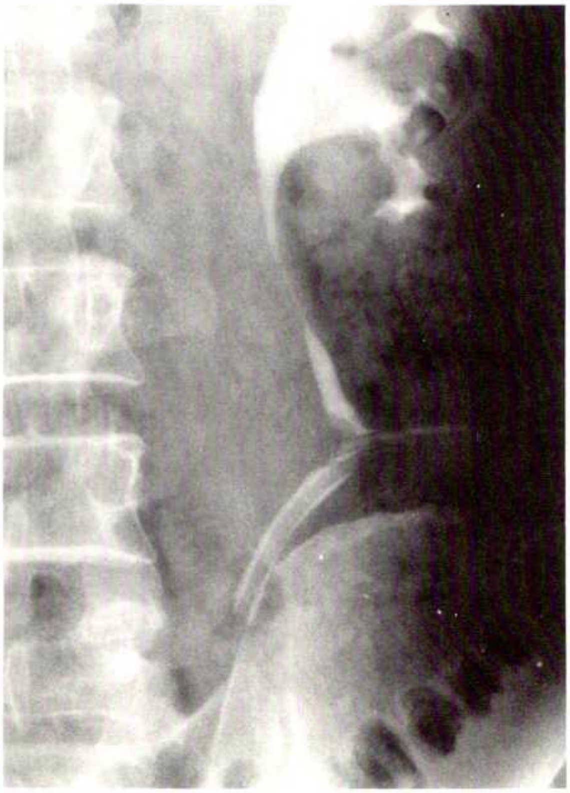
Points of Technique

Ureteroscopic Removal of a Retained "T" Tube Fragment

J. H. ANDERSON, D. KIRK and P. S. ORR, *Department of Urology, Hairmyres Hospital, East Kilbride, Glasgow*

A 48-year-old male with a 22-year history of renal calculi presented with renal colic. He had undergone left ureterolithotomy 6 years previously.

Intravenous urography demonstrated an opacity overlying the middle of the left ureter and hydronephrosis. A ureterolithotomy was carried out, with the insertion of a No. 10 ureteric "T" tube and a periureteric drain. One month later the "T" tube broke during removal, though no excessive force was used. The retained fragment folded and most of it lay outwith the ureter (Fig.). Using a ureteroscope, a Fogarty balloon tip catheter was manoeuvred into the "T" tube lumen and its balloon inflated. Traction was applied and the tube fragment was partly pulled out, but the fold in the fragment prevented it from negotiating the ureteric orifice. Using a ureterotome, the ureteric orifice was incised until the fold in the "T" tube was identified, caught with forceps and removed. A double J pigtail stent was inserted for 6 weeks and recovery was uneventful.



"T" tube ureteric stenting was used since this was a second ureterolithotomy. Percutaneous removal of the remnant would have been difficult because of the tube's displacement. Ureteroscopic techniques for retrieval of ureteric stents, avoiding further open surgery, have been described by Smith (1982). A cystoscopically introduced, Fogarty balloon catheter has been employed to remove a ureteric stent (Neindorf and Kalmi, 1975), using traction to avoid stretching and fracturing the tube. A combination of these methods was useful when removing the "T" tube.

References

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Smith, A. D. (1982). Retrieval of ureteral stents. *Urol. Clin. North Am.*, **9**, 109–112.

Requests for reprints to: P. S. Orr, Department of Urology, Hairmyres Hospital, East Kilbride, Glasgow H75 8RG.

Difficulty in Removing a Suprapubic Catheter

M. J. DIVERS and G. ROBERTSON, *Department of Urology, Leicester General Hospital, Leicester*

Case Report

A patient with adenocarcinoma of the sigmoid colon was admitted for anterior resection. Transurethral prostatic resection for benign adenoma had been performed 11 years previously.

Rectosigmoid anastomosis was technically difficult and a transverse colostomy was also fashioned. Since preoperative urethral catheterisation had been unsuccessful, a 16 F 2-wing Malecot catheter was placed extraperitoneally into the bladder dome, secured with a 2/0 Vicryl purse-string suture and brought out at the distal end of a midline incision. The catheter was clamped on the fifth post-operative day and urine passed normally. Attempts at removing the catheter 9 days post-operatively were unsuccessful. Plain X-ray excluded a catheter knot. At cystoscopy the catheter was not seen. A final attempt to remove it by traction resulted in the catheter breaking,

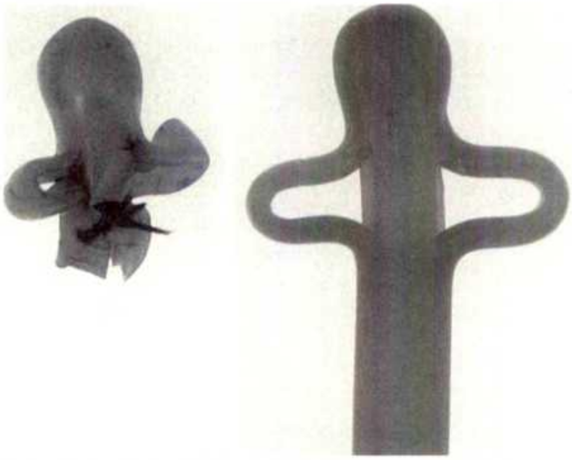

Fig. Catheter tip and suture adjacent to normal catheter.

leaving the tip in the abdominal wall. The lower end of the midline incision was opened and the catheter tip was seen to be caught securely in its Vicryl suture (Fig.) beneath the recti muscles.

Comment

Some suprapubic catheters are secured with balloons, some with Malecot tips and some are sutured to the abdominal wall. Previously reported difficulties in removing suprapubic catheters have involved breakage (Drutz and Koshid, 1984) and entanglement (Thornhill, 1985).

Our use of a Vicryl suture, which retains 75% of its tensile strength 14 days after insertion (Bucknall, 1987), had trapped the tip of the Malecot catheter. If a purse-string suture within the abdominal wall is thought necessary, one with minimal tensile strength at the time the catheter needs to be removed (such as plain catgut) should be used.

References

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Thornhill, J. A. (1985). Entangled urinary catheters—prevention of a "knotty" problem. *Br. J. Urol.*, **57**, 594.

Requests for reprints to: M. J. Divers, Department of Radiotherapy, Leicester Royal Infirmary, Infirmary Square, Leicester LE1 5WW.

British Journal of Urology (1989), 64, 107–108

Notices

C.-E. Alken Prize

An endowment fund has been established to further clinical work and research in the field of Urology by presenting an annual award of SwF 10,000 for outstanding scientific endeavours. The award will be for an unpublished work in the field of Urology. An award certificate will also be presented. The prize money may be divided among several contributors.

The papers may be written in either German or English and three copies must be submitted by 30 September 1989 to: Stiftungsrat C.-E. Alken-Stiftung, Advokaturbüro Dr F. Kellerhals, Bundesplatz 4, CH-3011 Bern, Switzerland.

Each submission must be affixed with a code word and must not bear the author's name. In addition, a sealed envelope labelled with the code word is to be included, containing on a separate sheet of paper the author's name and professional standing, together with the code word.

The adjudicators for the award will be the Board of Directors of the endowment fund and their decision will be final.

The Surgitek Prize

The Prize consists of a fully sponsored visit to the American Urological Association Annual Five-day Meeting, together with a tour of Surgitek's manufacturing facility in Racine, Wisconsin. It is open to trainees in urology and consultants who are within 5 years of first appointment. Entrants should submit a written paper, which may be on any subject, but must be unpublished, and must not have been submitted previously for the Surgitek Prize, or other prizes. The winning entry will be the one which is considered to be "The most significant contribution to urology".

Entries will be judged by three members of BAUS Council nominated at the October meeting of Council. Papers should be submitted in triplicate to the Honorary Secretary by 1 January each year.

Hans Marberger Prize

The Hans Marberger Prize will be awarded for the first time at the meeting of the German Urological Association in Hamburg in 1990. The prize, which will be donated by Karl Storz Ltd, will amount to öS 50,000 and will be awarded biennially for the best paper in the field of reconstructive surgery in urology or endourology. The award may be split.

Papers may be written in either German or English and should be submitted in triplicate to Dr H. Fuchshuber, Adamgasse 15, A-6020 Innsbruck, by 1 March 1990.

A code word should be affixed to each manuscript, which should not bear the author's name. In a separate envelope bearing the code word the following information should be given: author's first name, surname, position, and code word.

Edinburgh Urological Festival

A Joint Postgraduate Urological Meeting: Edinburgh University Department of Surgery (WGH) and Department of Urology, University of California, Davis

Edinburgh. 23–26 August 1989

The programme will consist of review lectures by invited speakers from the USA and Europe, with short papers by participants on the following topics: Superficial Bladder Cancer; Bladder Dysfunction; Reconstructive Surgery; Infertility and Sexual Dysfunction; Neo-adjuvant Chemotherapy; Flow Cytometry in Urology.

Further particulars from: Urological Festival Secretary, University Department of Surgery (WGH), Western General Hospital, Crewe Road, Edinburgh EH4 2XU, UK *or* Professor A. Stone, Department of Urology, University of California, Davis, Sacramento, USA.

Annual Meeting of the Swiss Society of Urology

Aarau, Switzerland. 21–23 September 1989

The main themes will be Renal Carcinoma and Ultrasound in Urology.

Further information from: Professor R. Tscholl, Urologische Klinik, Kantonsspital, CH-5001 Aarau, Switzerland, or Professor D. Hauri, Urologische Klinik, Universitätsspital, CH-8091 Zürich, Switzerland.

XXIII Annual Conference of the Urological Society of India

Ahmedabad, India. 21–25 September 1989

Further information from: Dr P. C. Patel, Organising Secretary, Dhananjay Nursing Home, Near Nagri Hospital, Ellisbridge, Ahmedabad 380 006, India.

Fourth Steglitz Pediatric Surgical Symposium: Laser Application in Children

Berlin, West Germany. 10 and 11 November 1989

Further information from: Dr Felix Schier, Department of Pediatric Surgery, Free University of Berlin, Hindenburgdamm 30, 1000 Berlin 45, West Germany.

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Manuscripts. Papers should be submitted in Journal style. Failure to do so may lead to significant delays in publication. Papers should be typewritten in double spacing on A4 paper (21 × 29.7 cm) with a margin of at least 3 cm all round. **Two copies of the manuscript and illustrations should be submitted** and the author should retain a copy for reference.

Authorship. All authors must give signed consent to publication. Only those who have made a substantial contribution to the work should be designated as authors and a maximum number of five is preferred. Those who have made a smaller contribution should be recognised separately in the Acknowledgements section.

Original articles should be set out as follows, with each section beginning on a separate page: title page, summary, text, references, authors' page, tables, legends to illustrations.

The *title page* should give the following information: (1) title of article, (2) initials and names of each author, (3) the department and institution to which the work should be attributed.

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REVIEW

The pT1 G3 Bladder Tumour

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In clinical practice a useful test result is one which allows a firm management decision. With respect to "superficial" bladder cancer—transitional cell carcinoma which has not invaded muscle—there are two questions which need to be asked of a bladder biopsy.

"Is there muscle invasion?"—in which case the patient may well be doomed despite subsequent therapy—and "Is there carcinoma *in situ* (CIS)?" In this latter case the incidence of progression to muscle invasive disease is sufficiently high to warrant treating the abnormal mucosa or even carrying out a prophylactic cystectomy. The chances of progression in extensive primary CIS are 60 to 80% in 5 years (Riddle *et al.*, 1976; Utz and Farrow, 1980), a level of risk where urologists on both sides of the Atlantic agree that an expectant policy is unacceptable except in the very elderly or infirm.

It is a paradox that the biopsy report is able to predict the likelihood of disease progression and yet it so rarely influences management. The decision is nearly always to repeat cystoscopic assessment in a few months.

Of those cases which progress from superficial to invasive disease, patients with primary CIS form less than 15% (Smith *et al.*, 1986). The majority of invasive tumours arise in patients with pT1 G3 disease. In the same series these comprised 18% of patients with superficial bladder cancer but produced approximately 60% of all those showing progression within 5 years.

How should this important group of patients be managed? Some surgeons point to the considerable risk of progression in pT1 G3 disease (Table 1) and to the low mortality of cystoprostatectomy in trained hands and recommend it at the outset. Most urologists in the UK, however, will think of the pleasures of life with a natural bladder and look for alternative management policies.

Patients with these tumours face 2 causes of premature death: from local recurrence of the primary lesion and from new high grade lesions arising from coexistent severely dysplastic epithelium. These threats merit separate consideration.

The Primary Lesion

pT1 G3 lesions are not common. The reported incidence varies from 6 to 23% of all superficial tumours (Table 2)—this being due largely to the variation in histological grading between different centres. Such tumours may be single or multiple, papillary or solid—the solid or polypoid appearance on endoscopy being more suggestive of G3 histology (Algaba, 1987; Jakse *et al.*, 1987).

Few reports address the problem of true recurrence (*i.e.* at the same site) following transurethral resection (TUR) of a pT1 G3 lesion. Two such studies have found local recurrence rates of 60% in 5 years and 22% in 2 years (Table 3). Presumably, tumour generating epithelium contiguous with the extirpated tumour remains after resection. If one cannot be confident that the resection has been wide enough it seems sensible to perform a further TUR about 6 weeks after the initial biopsy. This would also serve to avoid understaging tumours—a not infrequent (12–15%) occurrence (Bracken *et al.*, 1981; Lutzeyer *et al.*, 1982) which increases with increasing grade of disease (Utz and Farrow, 1980). Having removed the exophytic disease and checked that the remaining mucosa is free of CIS, is any further treatment to the bladder necessary?

TUR as a sole treatment

The incidence of recurrence (or new occurrence) following TUR is high but there appear to be some 20 to 30% of patients who are cured by the first

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Table 1 Superficial G3 Tumours Treated with TUR Alone: Progression

Author	*n*	*Stage*	*Progression (%)*	*Follow-up (months)*
Jakse *et al* (1987)	31	pT1	33	106
	23	pT1 (solitary)	29	106
	8	pT1 (multiple)	50	106
Heney *et al* (1983)	27	pT1	48	36
Smith *et al* (1986)	60*	pTa/pT1	39	60
Malmstrom *et al* (1987)	7	pT1	43	60
Pauwels *et al* (1988)	17	pT1 (G2b/G3)	35	24
Abel *et al* (1988)	24	pT1 (G2/3)	46	36
Ramsey J (Bart's series —personal communication)	8	pT1	63	72

*16 of these patients received intravesical agents.

Table 2 Superficial G3 Lesions—Incidence

Authors	*No.**	*Incidence (%)†*	
		pT1 G3	*pTa G3*
Jakse *et al* (1987)	172	23	—
Smith *et al* (1986)	299	18	1.6
Heney *et al* (1983)	249	11	1.6
Pauwels *et al* (1988)	122	6.5	—
England *et al* (1981)	332	8.4	—
Algaba (1987)	95	13	1.1
Malmstrom *et al.* (1987)	147	20	2.0
Abel *et al.* (1988)	107	5.6	2.8

*All pTa and pT1 lesions
†Percentage of all pTa and pT1 lesions

Table 3 Local Recurrence after TUR for PT1 G3 Disease

Authors	*Jakse et al* (1987)	*Wolf and Hojgaard* (1983)
No.	40	14
Further bladder tumours	80%	50%
Proportion with local (or local and distant) recurrences	0.74	0.43
True recurrence rate	60%	22%
Follow-up	5 years	2 years

TUR (Table 4). Given the high proportion of patients with coexistent CIS, the percentage of patients without field changes likely to remain disease-free may be greater than this figure, and for those given a "double" resection at the outset it may be higher still.

The progression rate for the series shown in Table 1 is roughly 40%. If we exclude from the denominator the proportion who develop no local recurrence—metastasis without local recurrence is very rare (Matthews *et al.*, 1984)—the progression rate for patients with recurrent disease in the bladder becomes 60%. This statistic is supported by Lutzeyer *et al.* (1982), who showed in a large study that the risk of progression in T1 disease was about double for a recurrent tumour compared with a primary one. This level of risk would, for many, justify a prophylactic cystectomy.

A policy of cystectomy on first recurrence would seem to have some merit, but a salutary warning is given by Malmstrom *et al.* (1987), who found that a muscle invasive tumour was the first sign of recurrence in 43% of patients who had progression from a superficial lesion.

Adjuvant intravesical chemotherapy

Given prophylactically following TUR of superficial transitional cell tumours (all grades), intravesical chemotherapy has been shown in controlled studies to increase the time to first recurrence and to reduce the number of recurrences, especially during the first 12 to 24 months (Herr *et al.*, 1987). There are, unfortunately, very little data yet on its efficacy in high grade disease.

A reduction in recurrence rate is useful in disease of low grade and stage, where the aim is to reduce the frequency of cystoscopy with its cumulative bladder trauma. In high grade disease the aim is the long-term prevention of progression to muscle invasive disease. No controlled study has yet demonstrated that intravesical chemotherapy can do this (Heney, 1988; Rubben *et al.*, 1988).

Table 4 pT1G3 Disease Treated with TUR Alone: Recurrence

Author	*n*	*Did not recur (%)*	*Follow-up (months)*
Algaba (1987)	12	33	26
Wolf and Hojgaard (1983)	14	50	24
Heney *et al* (1983)	31–33	21	36
Smith *et al.* (1986)	55*	25	60
Pauwels *et al.* (1988)	17 (G2b/G3)	52†	24
Abel *et al* (1988)	24 (G2/G3)	21	36
Jakse *et al* (1988)	30	20	60

*16 of these patients received intravesical agents.
†In first year.

It is possible that if a reduction in recurrence rate is achieved, the progression rate will also diminish; patients whose bladders are clear 1 year after starting chemotherapy with Epodyl have a very low progression rate, whilst the rate for those with persistent or recurrent disease is very high (Mufti *et al.*, unpublished observations). However, a review of controlled studies has shown that only 10 to 20% of patients benefit from prophylactic intravesical chemotherapy (Herr *et al.*, 1987). Furthermore, time to recurrence is delayed at most by 1 to 2 years in treated groups compared with controls. It is disappointing that in a study of 60 patients with pTa/pT1 G3 disease treated variously with mitomycin C, methotrexate and Epodyl, the progression rate was 40%—similar to that found in series where TUR alone was used (Smith *et al.*, 1986).

Intravesical chemotherapy is of unproven benefit in high grade disease. Moreover, it may be disadvantageous in that it delays recurrence to a time of low intensity surveillance when aggressive disease may be detected too late.

Radiotherapy

Radiotherapy can cure 21 to 31% of patients with T3 tumours and better results are obtained in T2 disease (26–57% cure rate) (Edsmyr, 1975, Plowman, 1985). It is to be expected that the cure rates for patients with T1 tumours will be higher still. In fact, the results of most series (Table 5) suggest that over 50% of patients subsequently remain progression-free. The very poor results of Sawczuk *et al.* (1988) probably reflect the use of radiotherapy following failure of intravesical chemotherapy. Bladder irradiation produces very little benefit in this situation and may also be poorly tolerated—2/30 of their patients required a cystectomy for bladder symptoms.

Where residual disease is left in the bladder before radiotherapy, the importance of inducing a complete remission is stressed by both Quilty and Duncan (1986) and Jenkins *et al.* (1988). Only 2 of 30 patients in this category subsequently progressed compared with all of 17 where there was no response.

Certainly recurrence of tumour following radiotherapy carries a very poor prognosis. In the series of 28 patients reported by England *et al.* (1981) there were 13 recurrences following radiotherapy; 11 of these had disease progression and 8 died of cancer; 7 of 11 progressions occurred in the first 2

Table 5 Radiotherapy for Superficial G3 Disease

Authors	*No*	*Stage*	*Progression-free (%)*	*Follow-up (months)*
Jenkins *et al.* (1988)	15	CIS+pT1 or pT2	60	36
Quilty and Duncan (1986)	31	pTa, pT1	56	60
Sawczuk *et al* (1988)	31*	pTa, pT1	30	n.s.
England *et al* (1981)	28	pT1	61	24
Malmstrom *et al* (1987)	11	pT1	46†	60
Ramsay *et al* (personal communication)	19	pT1	53†	48

*All had failed intravesical chemotherapy.
†Figures are for survival rather than freedom from progression.
n.s. Not stated.

years and cystoscopic surveillance should be regular during this time at least. Only 1 patient died of metastatic disease without local recurrence.

Analysis of Tables 1 and 5 raises the question of whether radiotherapy really improves the prognosis of patients with pT1 G3 disease. The sceptic's view that, as with intravesical chemotherapy, it clears the bladder of tumours which are unlikely to progress anyway cannot be refuted until a comparative study is carried out.

Cystectomy

The results of early cystectomy are impressive. Twenty-nine pT1 G3 patients who had the operation after a median of 2 TURs had an 88% 5-year survival rate (uncorrected) (Bracken *et al.*, 1981). In a large series of pT1 patients reported by the Mainz group (Stockle *et al.*, 1987), 55 patients (predominantly with G3 disease) who had a cystectomy on diagnosis had a 90% 5-year survival rate. They were compared with 18 patients in whom the operation did not take place until 1 or more recurrences had occurred. Here the 5-year survival rate was only 62%. Studies by Anderstrom *et al.* (1980) and Malmstrom *et al.* (1987) support this. It is hard to escape the conclusion that early surgery saves lives.

Coexistent carcinoma *in situ*

Multifocal carcinoma *in situ* is a frequent accompaniment of invasive bladder tumours (Koss, 1979). It is commonly associated with high grade superficial tumours (Table 6).

The progression risk of "secondary" CIS (*i.e.* associated with exophytic disease) may be slightly less than that for the primary variety—perhaps because it is not of such severity as to produce symptoms prior to diagnosis—but the risk is still 46 to 80% (Althausen *et al.*, 1976; Prout *et al.*, 1983; Herr *et al.*, 1986; Smith *et al.*, 1986).

Since the incidence of progression in patients with CIS is so high, it seems reasonable to assume that the majority of invasive tumours in these cases have arisen from the severely dysplastic epithelium. The possibility in pT1 G3 disease that all new superficial tumours distant from the original lesion arise from such coexistent CIS remains to be disproven. If this were indeed the case, control of the CIS should prevent distant "recurrences".

How should the urothelium be assessed for the presence of CIS? It is now well established that visual inspection alone is completely inadequate, for not only can the extent of disease be grossly underestimated (Utz and Farrow, 1980; Prout *et al.*, 1983), but areas of CIS and dysplasia can appear quite normal endoscopically (Cooper *et al.*, 1977; Heney *et al.*, 1978; Soloway *et al.*, 1978; Schade and Swinney, 1983; Wolf and Hojgaard, 1983; Vicente-Rodriguez *et al.*, 1987).

Random bladder biopsies should be performed—but there are traps here. It is important not to be misled by the absence of any mention of CIS on the biopsy report. All too often surgeons fail to heed the significance of epithelial loss on a biopsy specimen, a very common feature of CIS. It is in just such situations that urinary cytology proves to be an essential complement to mucosal biopsy. There should also be no reassurrance in the finding of "only" severe dysplasia. Whereas pathologists

Table 6 Incidence of Carcinoma in situ in Association with Superficial G3 lesions

			Incidence (%)		*Site*
Authors	*No*	*Stage*	*CIS*	*Other dysplasia*	
Algaba (1987)	12	pT1	67	8	
Heney *et al* (1978)	13	pTa, pT1	23	53	>36% adjacent to tumour
Siref and Zincke (1988)	32	pT1	66	n s.	
Soloway *et al* (1978)	12†	pT1	25*	25	
Cooper *et al* (1977)	13	pTa, pT1	23*	46	69% adjacent to tumour
Vicente-Rodriguez *et al* (1987)	37	pT1	54	n.s.	
Kakizoe *et al* (1985)	39	pT1	24	41	Adjacent to tumour
			12	34	Remote from tumour

*Includes pTa and pT1 lesions found on random biopsy, in addition to CIS.

†Does not include 6 patients with G3 lesions treated by cystectomy.

n.s. Not stated

may differ in what they mean by this term, the majority are describing features which have a prognosis identical to that of frank CIS.

There are some grounds for performing a biopsy of the prostatic urethra once CIS of the bladder has been established: 16% of patients with superficial bladder cancer relapse in the prostate (Soloway, 1988) and 40% of patients undergoing cystectomy for invasive transitional cell carcinoma have CIS of the prostatic epithelium (Montie *et al.*, 1986). Transurethral resection biopsy is both more sensitive and specific than fine needle aspiration or Tru-cut needle biopsy (Wood *et al.*, 1988). Whereas CIS of the prostatic urethra is reversible with intravesical BCG therapy, there is no evidence that this is so for CIS involving the prostatic ducts. Monitoring such disease is so problematical and the prognosis so poor once stromal invasion has occurred (Pugh, 1981) that affected patients are best managed by cystoprostatectomy.

CIS of the ureters may also be found. Twelve of 21 cystectomy specimens removed for apparently limited CIS of the bladder showed ureteric involvement (Utz and Farrow, 1980). The presence of such disease may be suspected when a patient with a normal IVU and bladder biopsies (*e.g.* following intravesical therapy) continues to have positive urine cytology. Ureteric urine cytology can be helpful in these circumstances.

The individual risks of progression of a pT1 G3 tumour and CIS of the bladder are high. Their association almost certainly compounds this risk, but conservative management may still be successful. Seven patients with this disease combination who were managed conservatively for periods of up to 5 years showed no evidence of progression. However, they may have been selected by a favourable response to intravesical agents (Prout *et al.*, 1983). In the same study it was found that the risk of progression in a larger group of patients was significantly lower in cases where CIS occurred after the original diagnosis of bladder cancer than in cases where the presentation was synchronous—presumably a temporal effect.

Whilst some patients with CIS may have a low risk of disease progression, the presence of a pT1 G3 lesion denotes the aggressive nature of the process and, except in patients with a short life expectancy for other reasons, treatment should be attempted.

Intravesical drugs and BCG

There are surprisingly few reports on the activity of cytotoxic drugs used intravesically against CIS of the bladder. Such reports as there are (Table 7A) suggest a complete response rate of 50%. There is very little information on the durability of these responses. In contrast, there are numerous reports on the use of intravesical BCG in this condition (Table 7B). Two studies with long follow-up suggest that normalisation of bladder epithelium can be achieved in 50 to 65% of patients for up to 5 years after treatment (Morales, 1984; Herr *et al.*, 1986). The latter authors in particular have demonstrated that BCG reduces the need for and prolongs the time to cystectomy.

Treatment is usually given as a course of 6 weekly instillations. There appears to be no benefit in

Table 7 Intravesical Agents for Carcinoma *in situ* of Bladder

Authors	*No*	*CIS*	*Complete response (%)*	*Follow-up (months)*	*Drug*
(A) Cytotoxic drugs					
Farrow *et al* (1977)	18	**	72	12–48	Thiotepa
Stanisic *et al* (1987)	24	**/‡	25	26	Thiotepa
Soloway (1988)	21	**	33	42	Mitomycin C
Stricker *et al* (1987)	19	**/‡	58	21	Mitomycin C
Jakse *et al* (1984)	15	**/‡	67*	42	Adriamycin
(B) BCG					
Herr *et al* (1986)	47	**/‡	68	36	†
Morales (1984)	17	**/‡	59	51	
Brosman (1985)	33	**/‡	82	50	
Catalona *et al* (1987)	29	**/‡	75	16	

*3/10 responding patients suffered a relapse of their CIS within 1 year of stopping treatment

†50% still in complete response at 5 years

** Primary CIS.

‡Secondary CIS

extending BCG treatment beyond 2 courses. Maintenance therapy serves only to increase the frequency and duration of side effects (Morales, 1984; Hudson *et al.*, 1987), whilst 80% of patients who have failed to respond to 2 courses will eventually develop progressive disease despite administration of a third course (Catalona *et al.*, 1987).

Intravenous cyclophosphamide

Cyclophosphamide is metabolised to reactive species in the liver and these pass into the urine, where they can be toxic to normal urothelium. The effect on malignant urothelium appears to be highly beneficial. Seventeen patients with primary CIS of the bladder received intravenous cyclophosphamide and three-quarters of these were disease-free at 3 months; 4 patients subsequently required further courses of cyclophosphamide but no responding patient developed invasive disease in the follow-up period of 3 or more years. On the other hand, 2 patients developed crippling bladder symptoms requiring cystectomy (Jenkins *et al.*, 1988).

Experience with cyclophosphamide in CIS is at present unique to the London Hospital. The simplicity of the treatment and its possibilities in the presence of upper tract disease are attractive.

Radiotherapy

The series of Riddle *et al.* (1976) and those reviewed by Whitmore and Prout (1982) provide good evidence that this treatment usually fails to control CIS of the bladder. However, a recent series from the London Hospital of radiotherapy in secondary CIS produced favourable results (Jenkins *et al.*, 1988). These findings may relate to disease extent—a factor known to be of prognostic importance (Riddle *et al.*, 1976)—since of patients with the same disease given no therapy at the same institution, very few progressed and some apparently resolved.

It is possible that patients with pT1 G3 disease who progress after radiotherapy (Table 5) are those with coexistent CIS (Wolf *et al.*, 1985). If so, perhaps such patients should not be treated with radiotherapy. However, work by Quilty *et al.* (1987) suggests that CIS on random biopsy gives no prognostic information as to durable local control or survival.

Cystectomy

The excellent results with early cystectomy for CIS are well known (Riddle *et al.*, 1976; Farrow *et al.*, 1977; Prout *et al.*, 1983). Thus patients with this condition who have failed two courses of BCG should, ideally, undergo such surgery.

Discussion

How should pT1 G3 disease be managed? From the above it is apparent that of the treatment approaches outlined, early cystectomy stands alone as a policy justifiable on the basis of good survival. If a more conservative approach is to be offered, it is important to identify those patients most likely to progress and offer them surgery.

Local recurrence following TUR is common and suggests that the initial resection was inadequate. For this reason we recommend that a second resection be performed at an early stage. Random biopsies can be performed simultaneously. In patients whose tumours subsequently recur locally, TUR alone is clearly insufficient and they should then be treated radically. Adjuvant radiotherapy

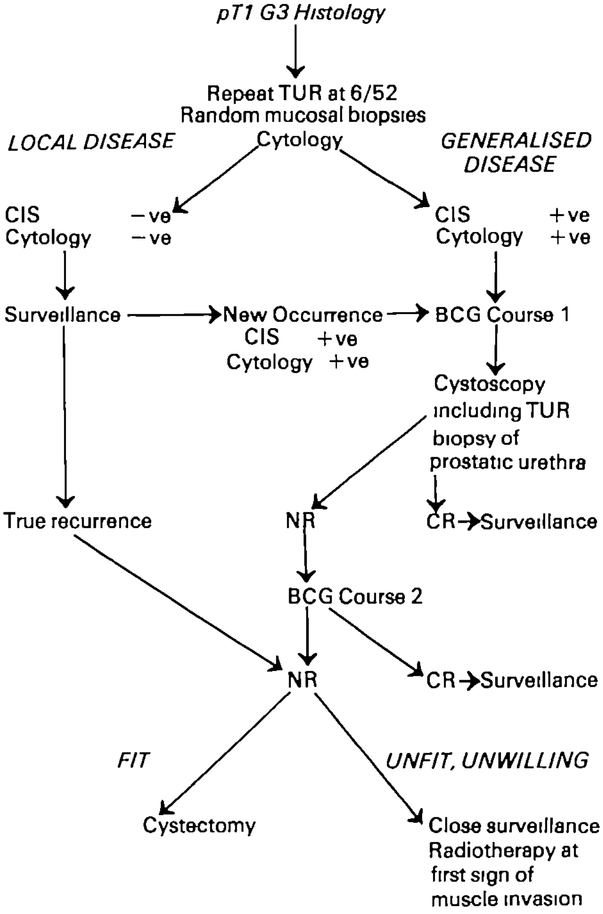

Fig. pT1 G3 lesion: management flow chart. CR = complete response. NR = no response following TUR may improve results but this needs to be tested in a randomised study.

Many patients with associated CIS are at considerable risk of developing new high grade tumours. The malignant epithelium can be normalised for long periods in some 50 to 60% of cases by intravesical BCG and this may well prevent new tumour development. However, where severe dysplasia persists after 2 courses, BCG therapy should be abandoned and the bladder removed, as shown in the algorithm (Fig.).

These procedures—the performance of a second resection with random biopsies and the administration of 2 courses of BCG with cystoscopic assessment after each—should take no more than 8 months. At the end of this period the patient should either have a normal urothelium or have lost his bladder.

Whitmore (1988) stated that the problem is to anticipate disease progression accurately enough to justify cystectomy at a time when the lesion is still amenable to local treatment. Early decision making in pT1 G3 disease will save lives without resorting to universal cystectomy. It is not uncommon for urologists to react to a pathological diagnosis of a pT1 G3 tumour in the same manner as for a pTa G1 lesion: check cystoscopy in 3 to 4 months. Available evidence suggests that this is no longer appropriate.

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Extracorporeal Shock Wave Lithotripsy with the Lithostar Lithotriptor

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Summary—Early experience of extracorporeal shock wave lithotripsy (ESWL) using the Lithostar lithotriptor is reported; 145 patients underwent 185 treatments for 189 stones. Treatments were performed with either intravenous sedation and analgesia (90%) or general anaesthesia (10%). There were 123 renal calculi, 44 ureteric calculi and 22 staghorn calculi. Stone fragmentation was achieved with 1724 ± 1035 shocks at 19 kv. The immediate stone fragmentation rate was 90% and the 3-month clearance rate 88%. Secondary treatments were required in 19% of patients and additional procedures in 17%. A comparison between stone size and the number of shock waves required to achieve stone fragmentation revealed a linear relationship. The Lithostar is a very effective second generation lithotriptor which can be used for renal, staghorn and ureteric calculi *in situ*, without manipulation.

Extracorporeal shock wave lithotripsy for renal calculus disease was first introduced into clinical practice by Chaussy *et al.* (1980). The technique rapidly gained acceptance and is now the treatment of choice for renal calculi measuring up to 2–3 cm (Drach *et al.*, 1986). ESWL has also been used to treat ureteric calculi either *in situ* (Miller and Hautmann, 1987) or following manipulation of the stone into the kidney: the "push and bang" technique (Coptcoat *et al.*, 1987; Lingeman *et al.*, 1987; Evans *et al.*, 1988). More recently, the indications for ESWL have been extended to include the treatment of staghorn calculi either as monotherapy or in combination with percutaneous nephrolithotomy (Eisenberger *et al.*, 1987; Winfield *et al.*, 1988).

While the Dornier HM3 lithotriptor dominated early experience with ESWL, a number of modifications and improvements led to the introduction in 1986 of the second generation lithotriptors. Prominent among these instruments was the Siemens Lithostar. We have used the Lithostar in the management of renal calculi, ureteric calculi *in situ* and as monotherapy for staghorn calculi. Furthermore, we have attempted to correlate stone size with the number of shock waves required to achieve fragmentation.

Patients and Methods

The Lithostar incorporates an electromagnetic shock wave source which allows local coupling of the shock head to the patient, thus eliminating the need for a water bath. A slab coil is separated from a metal membrane by a thin insulating layer. When a high voltage pulse from a capacitor discharge is passed through the coil it induces a current in the membrane. The membrane is rapidly repelled by the coil, resulting in the generation of parallel pressure or shock waves. These waves are propagated through a water-filled cylinder at the speed of sound and focused by means of an acoustic lens system (Fig. 1). The intensity of the shock wave produced is directly proportional to the current pulse passed through the coil. Local coupling of the shock head to the patient's flank is achieved by means of a soft silicone coupling head. Two shock heads are available for separate treatment of right- and left-sided stones.

Localisation of the stone is accomplished by means of 2 standard X-ray units positioned in

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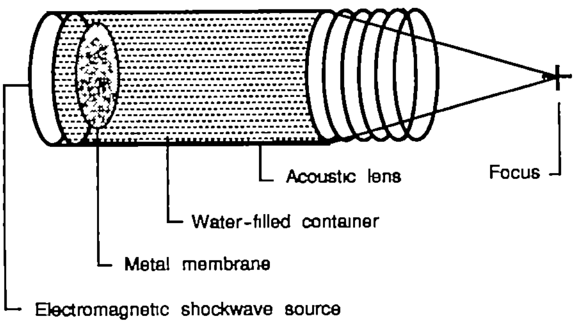

Fig. 1 Schematic representation of the shock head of the Lithostar Shock waves, generated by an electromagnetic source, are transmitted through a water-filled cylinder and focused by means of an acoustic lens.

antero-posterior and oblique planes. The patient is moved in 3 axes by means of a standard radiological table top which can also be adapted to endourological procedures. Normal cassette films can be obtained with the antero-posterior X-ray unit. Shocks are normally delivered at a frequency of 100 shocks/min at a maximum generation voltage of 19 kv. A facility for respiratory and ECG triggering of shocks is available which makes for more accurate and safer ESWL.

There was no selection of patients and all who were referred to the lithotripsy unit underwent ESWL. Before treatment, each patient underwent investigations which included baseline laboratory data, urine analysis and urine culture, plain films of the abdomen and an intravenous urogram. No cystine or uric acid stones were found and no stone was considered too large for ESWL monotherapy. At the end of the procedure a plain abdominal radiograph was obtained. All patients had plain abdominal films and renal ultrasonography performed on the first day after ESWL. They were reviewed at monthly intervals or until the stones were completely cleared. Stone clearance was defined as the absence of fragments on a plain abdominal radiograph.

Results

Between October 1987 and June 1988, 130 patients underwent 168 treatments for 166 stones. Their mean age was 44 years (range 2½–78); 44% were male. ESWL was performed with sedation and analgesia (medazalam and fentanyl) in 117 patients (90%) and under general anaesthesia in 10 (8%). These were either children or patients undergoing endourological procedures. The remaining 3 patients (2%) required no anaesthesia. In none of our patients was local or epidural anaesthesia employed.

There were 123 renal calculi (65%); 40 stones (21%) were in the renal pelvis and 84 (44%) were in the upper, middle and lower calices. Of the 44 ureteric calculi (23%), 31 were sited in the ureter above the pelvic brim (16%) and 13 were in the distal ureter (7%). Nineteen patients (10%) underwent ESWL for 22 staghorn calculi (Table 1). The overall mean stone size was 1.3 cm, with staghorn calculi having a mean size of 4.6 cm. A total of 27 patients (19%) required repeated treatments. Secondary treatment was performed as a planned procedure for several of these patients, including 14 (10%) with staghorn calculi. The mean number of shock waves/treatment was 1724 for all stones and 2325 for staghorn calculi. However, since many patients with staghorn calculi underwent secondary treatment, the mean shock waves delivered/patient in this group was 6000. Immediate stone fragmentation was achieved in 90% of treatments and 65 of the 74 patients (88%) followed up for 3 months were clear of stones (Table 1). Additional procedures were performed in 24 patients (17%); a double-J catheter was inserted endoscopically in 11 patients, a percutaneous nephrostomy was performed in 3, ureteroscopy to extract fragments in 5 and uretero- or pyelo-lithotomy in 2 patients. Pain or pyrexia developed in 17 patients (12%) following ESWL and 2 patients, both with staghorn calculi, developed septicaemia. One of these responded to intravenous antibiotics but the other required an

Table 1 Results of ESWL with the Siemens Lithostar

	Patients	*Stones*	*Rx*	*Shocks/Rx*	*Immediate fragmentation (%)*	*Clearance at 3 months (%)*
Renal	87	123	94	1793±651	84/94 (89)	35/39 (90)
Ureteric	39	44	40	1656±890	37/40 (92)	23/27 (85)
Staghorn	19	22	51	2325±1600	45/51 (88)	7/8 (83)
Total	145	189	185	1724±1035	166/185 (90)	65/74 (88)

emergency nephrolithotomy, having failed to respond to a percutaneous nephrostomy. A "steinstrasse" was seen in 6 patients (4%) and transient haematuria in 6. One patient who had undergone ESWL for an upper ureteric calculus developed haemoptysis, with no evidence of pneumonia or pulmonary embolus. All patients had a postoperative renal ultrasound scan but none was found to have a perirenal or intrarenal haematoma. During ESWL with fixed frequency application, occasional extrasystoles developed in 13 patients (9%). These were easily managed by the application of ECG triggering.

To analyse the relationship between stone size and the number of shock waves required for stone destruction the greatest diameter of each stone was measured. The stones were divided into 4 groups (0–0.9 cm, 1–1.9 cm, >2 cm, staghorn) and these were compared with the number of shock waves required for destruction. The results are presented in Table 2 and Figure 2. A strong positive correlation existed between stone size and shock waves delivered (r = 0.96), indicating that larger stones require more shock waves to achieve fragmentation.

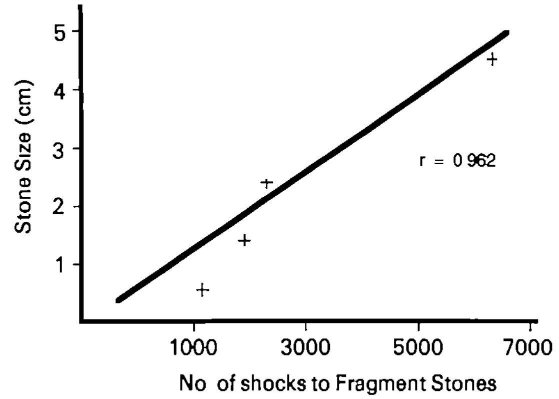

Fig. 2 A positive correlation exists between stone size and the number of shocks required to fragment the stones (r = 0.962)

Discussion

This analysis indicates that the Lithostar is a very effective second generation lithotriptor with an immediate stone fragmentation rate of 90%, a 3-month clearance rate of 88% and an extra procedure rate of 17%. Wilbert *et al.* (1987), also using the Lithostar, observed an immediate stone disintegration rate of 96%. Of 413 patients available for follow-up at 3 months, 397 (96%) were free of stone or had small residual fragments. Our results compare favourably with their secondary treatment rate of 12% compared with the 19% and 17% secondary treatment and auxiliary treatment rates, respectively, observed in the present report. The figures in this report include results in staghorn calculi >3 cm in diameter. Drach *et al.* (1986), reporting a co-operative study of 2112 patients using the Dornier HM-3 lithotriptor, observed an immediate stone fragmentation rate of 92% and a 3-month clearance rate of 66%. Their auxiliary procedure and secondary treatment rates were similar to those of the present study at 17 and 16% respectively. Rassweiler *et al.* (1987) reported successful stone disintegration in 94.5% of patients with the Wolf Piezolith 2200. The auxiliary procedure rate (25%) and secondary treatment rate (57%) were considerably higher with this lithotriptor. The piezoelectric system has the advantage that ESWL can be performed without anaesthesia or sedation. In relation to stone disintegration and secondary procedures, the results of this study compare favourably with the results of other ESWL series (Table 3).

Table 2 Correlation between Stone Size and Shock Waves Delivered to Achieve Stone Fragmentation

	0–0.9 cm	*1.0–1.9 cm*	*>2.0 cm*	*Staghorn*
Stone size	0.6±0.2	1.2±0.3	2.4±0.7	4.6±1.7
Shocks	1200±560	1790±652	2107±903	5943±4088

The role of ESWL in the management of ureteric

Table 3 Comparison of Results of ESWL using Different Lithotriptors

	Stone disintegration (%)	*Auxiliary procedures (%)*	*Secondary treatments (%)*	*Clearance at 3 months (%)*
Dornier HM-3 (Drach *et al.*, 1986)	92	17	16	66
Wolf Piezolith (Rassweiler *et al*, 1987)	94	25	57	—
Lithostar (Wilbert *et al.*, 1987)	96	12	12	96
Lithostar (Present study)	90	17	19	88

calculi is controversial. Chaussy and Schmiedt (1984) reported a 95% stone clearance rate for proximal ureteric calculi treated *in situ* without manipulation of the stone into the renal pelvis. Lingeman *et al.* (1987) failed to confirm these observations and advocated that proximal ureteric calculi should be manipulated back into the kidney prior to ESWL. Coptcoat *et al.* (1987) and Evans *et al.* (1988) also supported the use of ureteric catheterisation and retrograde irrigation of ureteric calculi prior to ESWL. Evans *et al.* (1988) noted that a marked increase in total power (number of shocks × kv) was required to fragment ureteric calculi *in situ* (2400 shocks at 26 kv) compared with ureteric calculi following manipulation into the kidney (1700 shocks at 21 kv). All of these authors used the Dornier HM-3 lithotriptor. However, in the present study, using the Lithostar, all ureteric calculi were treated *in situ* without initial manipulation. There was a 92% immediate fragmentation rate in the 31 patients with proximal ureteric calculi. This was achieved by applying 1635 ± 872 (mean ± SD) shocks at 19 kv. This compares favourably with the 1793 ± 651 shocks at 19 kv required to fragment renal stones in our analysis. Some authors have suggested that a 95% success rate can be achieved with ESWL for distal ureteric calculi, although a higher total power is required (Miller and Hautmann, 1987; Becht *et al.*, 1988). Our experience with distal ureteric stones is small but we achieved 100% fragmentation in the 13 patients we have treated to date, applying 1822 ± 913 shocks at 19 kv. By placing the patient in the prone position, mid-ureteric calculi can also be treated with ESWL using the Lithostar, and we advocate ESWL as the treatment of choice for all ureteric calculi.

The indications for ESWL have been extended to include the treatment of staghorn calculi (Fuchs and Chaussy, 1987). Controversy has existed as to whether ESWL monotherapy or ESWL in combination with percutaneous nephrolithotomy (PCN) should be the treatment of choice for these stones. In a recent study comparing ESWL monotherapy using the Dornier HM-3 lithotriptor with PCN monotherapy, Winfield *et al.* (1988) observed a 61% stone clearance rate at 8 months for ESWL compared with 76% for PCN. However, operating time and morbidity were both less for ESWL. Although our initial experience of staghorn calculi is small, our results indicate that at 3 months an 83% clearance rate (7 of 8 patients) can be achieved with ESWL monotherapy using the Lithostar. Thus, while we would agree with Winfield *et al.* (1988) that PCN and ESWL should be viewed as complementary procedures, we would argue that ESWL monotherapy has a role in the management of staghorn calculi.

Concern has been expressed about the safety of ESWL and the number of shocks which should be administered to achieve stone fragmentation. Kaude *et al.* (1985) documented haematuria in all of their patients after approximately 200 shocks. Using magnetic resonance imaging, the same authors also detected morphological abnormalities in 63% of patients immediately after ESWL. In contrast, Chaussy and Schmiedt (1984) observed subcapsular haematomas in only 0.6% of patients following ESWL. In the present analysis we detected no parenchymal or subcapsular haematomas and only 4% of our patients developed haematuria. Drach *et al.* (1986) reported 4 deaths within 6 weeks of ESWL, 2 of which were related to hypertension. The implications of these findings remain unclear and it would seem prudent to administer only the number of shocks required to achieve stone fragmentation and to avoid "overkill" by giving excessive numbers of shocks which might result in renal damage. In the present analysis we have demonstrated a linear relationship between stone size and shock waves required to achieve fragmentation. Although stone density is clearly important, we suggest that stone size can be used to predict the number of shock waves which should be administered.

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Allograft Nephrectomy—a 16-year Experience

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Summary—A review has been made of the indications, technical problems, complications and results of 31 allograft nephrectomies in 29 patients; 12 patients died between 15 days and 1 month after graft nephrectomy, which was undertaken within 6 months of transplantation.

Gross local and general complications occurred in 7 patients who survived graft nephrectomy. The procedure is recommended when graft failure occurs within 6 months of transplatation provided it is associated with systemic signs of severe rejection or sepsis, or if it occurs in cases where continuation of immunosuppressants is life-threatening.

In many transplant centres it has been considered obligatory to remove a failed renal allograft, since such grafts are regarded as a potential hazard to the patient (Gustafson *et al.*, 1973). At our centre this has been done only following specific indications, since the procedure is associated with a high incidence of mortality and morbidity.

Patients and Methods

A total of 675 live kidney transplants were performed in 653 recipients between 1971 and 1987; 20 recipients received a second graft and 2 had a third graft.

We performed 31 allograft nephrectomies in 29 patients (21 male and 8 female, age range 15–42 years). Twelve patients had a second transplant within 6 months of graft nephrectomy; 3 patients who were given a second transplant required a second allograft nephrectomy. The procedure was carried out within 6 weeks of transplantation in 13 instances (Table 1); 3 kidneys did not function at all and were removed because of acute rejection; 2 patients had accelerated rejection and 3 developed severe acute rejection.

In 3 cases the graft was removed because of secondary haemorrhage from the anastomotic suture line. This was associated with wound infection. A non-functioning pyonephrotic kidney was removed in 1 patient and in another graft nephrectomy was carried out for renal vein thrombosis.

On 17 occasions, grafts were removed between 6 weeks and 6 months after transplantation, the major cause being graft sepsis (10 cases); 7 patients had irreversible acute rejection. One patient underwent allograft nephrectomy due to chronic rejection more than 6 months after transplantation.

The operation was performed under general anaesthesia or spinal analgesia. All grafts were re-explored through the original transplant incision. Extracapsular removal of the graft was performed in 30 cases: in 1 case a subcapsular nephrectomy was carried out. All 31 patients had end-to-end internal iliac and renal artery anastomoses and end-to-side renal vein to external iliac vein anastomosis. In 29 cases the blood vessels were separately identified and the artery was ligated proximal to the earlier transplant anastomoses and then divided. Because of the friability of the renal vein we prefer to detach the renal vein from the external iliac vein and oversew the opening in the external iliac vein with 5/0 silk or 5/0 prolene. In 1 case, *en masse* ligation was done; in another there was profuse haemorrhage and therefore the common iliac artery was ligated. In difficult nephrectomies the peritoneum was deliberately opened to identify the common iliac and internal iliac arteries. The wound was routinely closed with a tube drain connected to dependent drainage.

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Table 1 Indications for Allograft Nephrectomy (Total Patients = 31)

Within 6 weeks after transplantation		*6 weeks to 6 months after transplantation*		*More than 6 months after transplantation*	
Hyperacute rejection	3	Irreversible acute rejection	7	Chronic rejection	1
Accelerated rejection	2	Graft sepsis	10		
Severe acute rejection	3				
Secondary haemorrhage (cause-wound infection)	3				
Renal vein thrombosis	1				
Non-functioning pyonephrotic graft	1				

In the first 10 cases, 1 g chloramphenicol (diluted in 500 ml normal saline) was used for wound irrigation because of its highly specific effect on anaerobic micro-organisms. We now use a 1:10 solution of povidone iodine for this purpose. If there has been excessive graft infection with wound contamination, we wash the wound with a 10 volume strength of hydrogen peroxide before irrigation with povidone iodine.

For prophylactic purposes, 1 g cloxacillin and gentamicin (3 mg/kg body weight i.v.) is administered per-operatively. Azathioprine was discontinued immediately after graft nephrectomy but patients received prednisolone 10 mg/day thereafter. We use prednisolone and azathioprine for immunosuppression. Cyclosporin A is used in specific situations, mainly those involving children, diabetics and in patients undergoing a second transplantation.

Before 1983, we were giving corticosteroids in doses of 240 mg/day for the first week, reducing the dose to 60 mg/day in the second week. At present we use 100 mg prednisolone/day for the first week and reduce the dose to 40 mg/day by the second week.

Results

There was no operative mortality. A total of 12 patients died between 15 days and 1 month after graft nephrectomy; 9 died following the first transplant, of whom 2 died of secondary haemorrhage; 5 developed fulminant septicaemia and 2 had sudden cardiac arrest on the second day during dialysis. Death in the latter was possibly due to pulmonary embolism. Of the 3 patients who died after a second transplant, 1 died whilst on dialysis within 1 month of graft nephrectomy due to cytomegalovirus infection. The second died 10 months after graft nephrectomy, while on dialysis, (possibly due to septicaemia). The third patient died of pericarditis and wound sepsis within 10 days of graft nephrectomy.

The remaining patients who had a second transplant are doing well and are on conventional immunosuppressive therapy. Two patients who had a third transplant are doing well (Table 2).

Of the patients who survived, gross wound infection occurred in 3, 1 had wound haematoma, and transient post-nephrectomy haematuria developed in 1 patient; 2 had pulmonary tuberculosis and 1 had extreme cachexia (Table 3).

Discussion

Problems related to allograft nephrectomy are basically 3-fold. The first is that definite criteria for the removal of a failed graft are not yet clearly defined. Schweizer *et al.* (1973) perform nephrec-

Table 2 Mortality After Graft Nephrectomy

Cause	*No of patients*
Secondary haemorrhage	2
Fulminant septicaemia	5
Death during dialysis	2
Death after second transplant	
CMV infection	1
Septicaemia	1
Pericarditis	1
Total	12

Table 3 Morbidity in Patients Who Survived After Graft Nephrectomy

Complications	*No. of patients*
Gross wound infection	3
Wound haematoma	1
Transient post-nephrectomy haematuria	1
Pulmonary tuberculosis	1
Profound loss of weight	1
Total	7

tomy as soon as the renal scan indicates insignificant blood flow to the graft in the belief that this reduces the incidence of wound infection. Najarian (1974) suggested early nephrectomy because failed transplanted kidneys (as a result of continuing immunosuppression) are frequently the source of local or systemic infection.

Sinha and Castro (1976), in their series of 54 allograft nephrectomies, suggested that indications for early graft removal included local signs and symptoms related to the graft, graft infection and severe uncontrolled hypertension. These symptoms are most likely to occur soon after non-function of the allograft and early nephrectomy is encouraged in such cases.

The second problem is related to the fact that surgical exposure of these kidneys is very difficult because of extensive adhesions related to rejection, sepsis or both. A knowledge of the previous vascular anastomoses is crucial. Previous end-to-end arterial anastomoses are probably more easily dealt with than end-to-side anastomoses.

The third problem is wound infection; 8 patients (20%) developed wound infection in a series reported by Sinha and Castro (1976). In other series, the rates of infection ranged from 17 to 56% (Moore and Hume, 1969; Schweizer *et al.*, 1973).

In the present series only 3 patients (13.4%) had gross wound infection. This was associated with secondary haemorrhage in 2 cases. The organisms isolated were *Pseudomonas aeruginosa* and *Staphylococcus aureus*.

The problem of wound infection is almost universal and is compounded by formation of haematoma due to early dialysis, difficulty in closing the dead space and poor immunological resistance. The Penrose drain has also been implicated as a foreign body and a conduit for surface bacteria to enter the wound. The increased incidence of wound infection may be the result of over-enthusiastic use of immunosuppressants. High doses of steroids, as previously used, not only delayed wound healing but also produced other complications. The continued use of azathioprine will accelerate the problem of wound sepsis and infection due to leucopenia.

Early allograft nephrectomy is associated with considerable mortality and morbidity which is frequently the result of the patient's poor general condition and pre-existing infection. This is compounded by the fact that severe rejection is superimposed on this clinical situation.

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Relationship between Intermittent Hydronephrosis and Megacalicosis

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Summary—Intermittent hydronephrosis is notoriously difficult to diagnose but, once confirmed, requires surgery. In contrast, congenital megacalicosis is accepted as a non-obstructive cause of upper urinary tract dilatation for which surgery is inappropriate. Experience with 2 cases and a review of the literature suggest that occasionally the clinical features and radiographic findings in the 2 conditions may overlap, leading to misdiagnosis. Attention to the combination of clinical features and radiography, together with the use of radionuclide techniques and acute pain studies, may help to distinguish between these conditions.

Congenital megacalicosis was first described by Puigvert in 1963. Intravenous urography in affected patients shows dilatation of the renal calices, but the renal pelvis is undilated and funnels into a dependent ureter of normal calibre (Fig. 1). Although uncommon, megacalicosis has become accepted as a benign condition which does not require surgery; it can be regarded as one of the many examples of conditions comprising non-obstructive dilatation of the upper urinary tract (O'Reilly, 1986). However, some patients showing classic radiological features suggestive of megacalicosis may not be entirely immune to obstructive episodes.

Case Reports

Case 1. A 20-year-old man presented to the urological clinic complaining of intermittent, infrequent, but severe discomfort in the left loin. There were no obvious precipitating factors, such as beer drinking, and no associated symptoms. The pain would present unpredictably, last for a few hours, or occasionally a day, and then subside spontaneously. The patient was anxious to know the diagnosis and concerned because he was having to take time off work. Examination revealed a healthy normal male. Urine analysis and haematological and biochemical blood tests were normal. Since the intravenous urogram showed dilated calices but only a minimally distended renal pelvis with a dependent ureter, the possibility of megacalicosis was considered (Fig. 2A). Gamma camera diuresis renography showed a dilated non-obstructed washout pattern with normal split renal function (Fig. 2B). It was explained to the patient that no abnormality deserving of surgery had been found. However, he was instructed to contact the department if

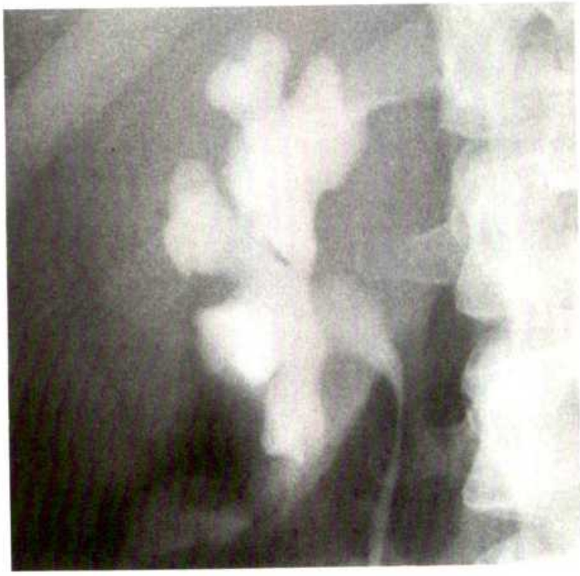

Fig. 1 Primary Megacalicosis of right kidney.

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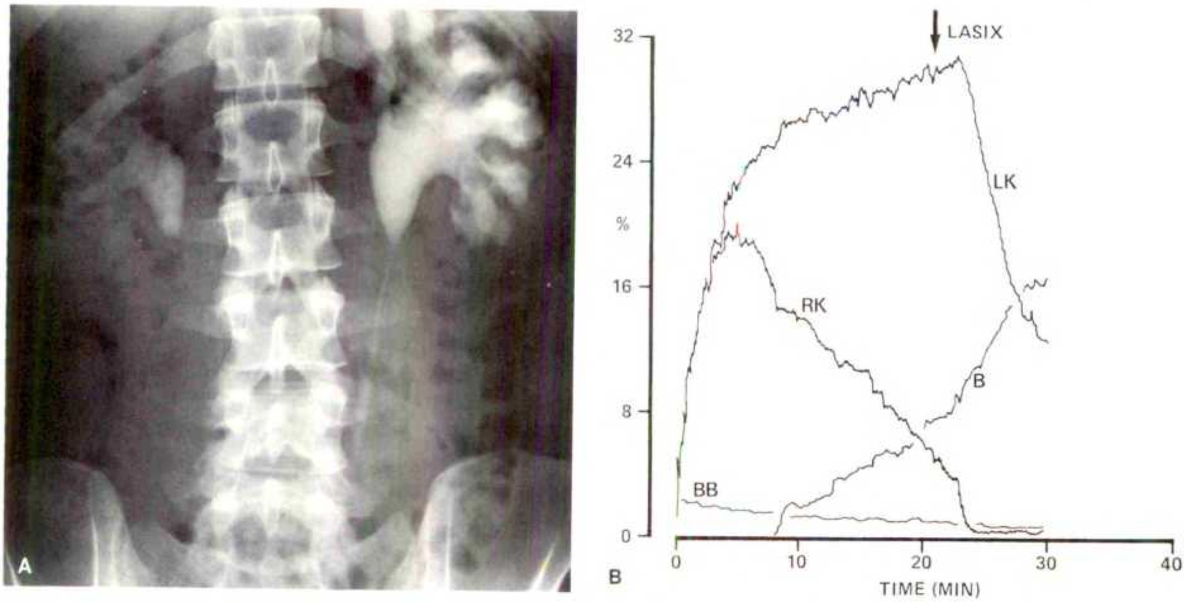

Fig. 2 (A) Urogram in case 1 showing dilatation of the calices of the left kidney but a normal renal pelvis funnelling down into a dependent ureter. (B) ^{123}I-hippuran gamma camera renogram showing dilated non-obstructed response with excellent washout under diuretic provocation.

he suffered further pain so that he could be assessed in the acute phase. He returned some weeks later with severe pain. Urography showed significant pelviureteric junction obstruction (Fig. 3A) and gamma camera renography showed deterioration in diuretic washout (Fig. 3B). The patient had an Anderson-Hynes pyeloplasty. Post-operative diuresis renography showed a non-obstructive pattern.

Case 2. A 62-year-old female complained of intermittent but infrequent right loin pain. Intravenous urography showed megacalicosis (Fig. 4A) with marginal dilatation of the renal pelvis. The possibility of equivocal mild obstruction was raised on diuresis renography (Fig. 4B). The patient's symptoms were infrequent, however, and she was followed up by interval renography, which remained unchanged over 12 months. At this point her symptoms increased, washout deteriorated marginally and split renal function showed a significant fall from 52 to 32% (Fig. 4C). Perfusion pressure flow studies had been attempted but accurate needle placement had failed. It was decided, on the basis of the sub-total renogram washout, convincing renal pain and deteriorating split function, to explore the kidney. At operation the renal pelvis was found to be small, non-compliant and not obstructed to the naked eye. The ureter was dependent and uncompromised by kinks or aberrant vessels. The renal pelvis was cannulated and filled slowly with saline. Initially, hyperperistalsis occurred with effective transmission to the ureter; then tubular flow down the ureter was produced, ureter and pelvis both being distended. However, the renal pelvis suddenly became acutely distended, pelvic peristalsis ceased and the ureter collapsed, giving the classic appearances of hydronephrosis secondary to pelviureteric junction obstruction. No change occurred during several minutes' observation. The ureter was divided just below the pelviureteric junction but no urine flowed from the decompensated pelvis. An Anderson-Hynes pyeloplasty was performed and the patient became symptom-free. Post-operative diuresis renography showed non-obstructed appearances with split function of 52%.

Discussion

The non-obstructive nature of primary megacalicosis is widely accepted (Gittes and Talner, 1972; Johnston, 1973, 1982). Johnston (1973, 1982) reported that the overlying parenchyma was often thinned but Gittes and Talner (1972) believed the renal cortex to be normal, but stretched around the dilated calices. There is usually delayed filling of these dilated calices, whose number can be increased from 8–12 to as many as 20–25. Angiography is normal apart from the stretching of vessles around the dilated calices. The aetiology of the condition is unknown. Gittes and Talner (1972) suggested that it was due to developmental hypoplasia of the renal pyramids, of unknown causation, while Johnston (1973) suggested similarities be-

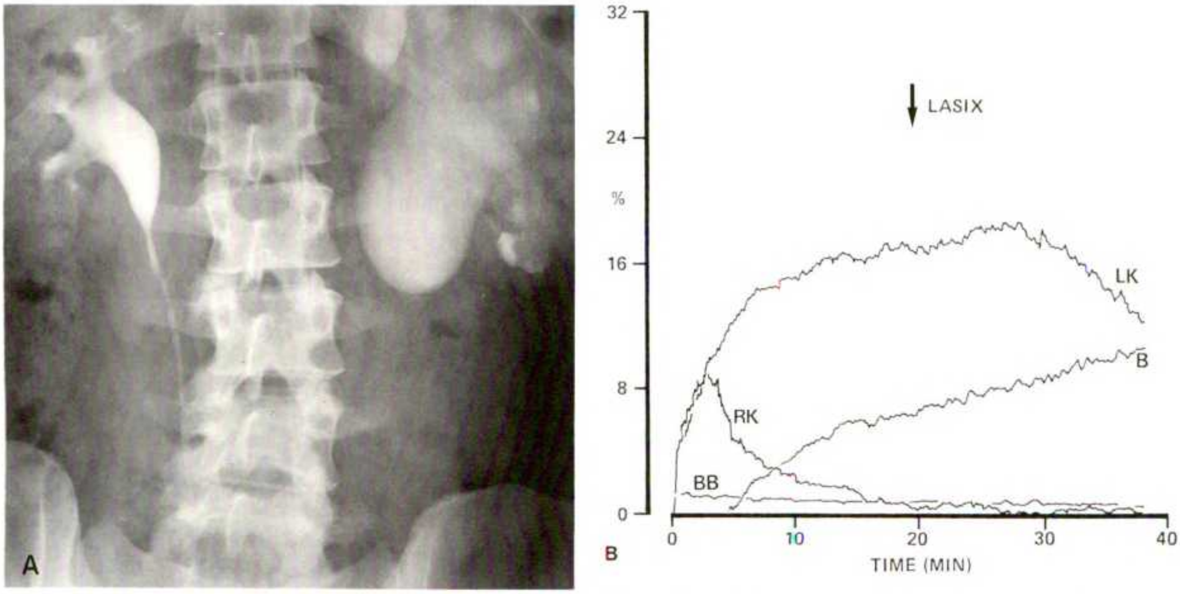

Fig. 3 (A) Acute pain IVU in same case showing pelviureteric junction obstruction. (B) Post-urography acute pain ^{123}I-hippuran gamma camera renogram showing delayed, incomplete, poor washout under diuretic provocation, with marked deterioration over previous study.

tween this condition and the appearances in cases of hydronephrosis caused by persisting ureteric fetal folds, attributing the condition to "burnt-out" obstruction following spontaneous involution of the folds.

The ages of reported patients have been 5 to 60 years, with a male to female ratio of 10:1. Radiographic appearances and renal function have remained stable in cases followed over several years, although a mild distal tubular concentrating defect has been demonstrated (Galien *et al.*, 1970). Occasionally a wide ureter is found and infection and stones may occur. Whitaker and Flower (1981) reviewed 10 patients with primary megacalicosis, all of whom had perfusion pressure flow studies; 8 had no evidence of obstruction but 2 did show such evidence, though in neither could the site of obstruction be demonstrated. Both were followed conservatively; 1 showed no radiological changes over 7 years while the other had 2 further attacks of pain over several years and one episode of haematuria, but no radiological deterioration at the time of reporting. Aaronson (1980) reported 3 similar cases which he described as "compensated hydronephrosis" but whose radiological findings as presented were suggestive of primary megacalicosis. Direct-puncture pelvic pressure studies showed high pressure contraction waves which resulted in pelvic emptying, although basal pressures were normal. He suggested that in these cases the thicker walled renal pelvic musculature might retain its tone in the presence of the high pressure contraction waves, but the thinner walled calices were unable to do so and became and remained dilated.

The 2 cases reported here showed features suggestive of primary megacalicosis and they were not initially thought to be candidates for surgery. However, persisting intermittent symptoms in each stimulated close follow-up. In the first, an acute pain IVU led to the diagnosis of intermittent hydronephrosis; in the other, persisting symptoms and deteriorating function stimulated surgical exploration, when the diagnosis of intermittent hydronephrosis was confirmed. Both patients had dismembered pyeloplasty.

Intermittent hydronephrosis was first described by Nesbit (1956) in patients who were having acute attacks of pain but whose pyelograms were normal between attacks. The precipitating factors which cause the sudden painful obstructive episodes in such cases are not known (Jacobs *et al.*, 1979), nor is any provocative test guaranteed to reveal the underlying abnormality. Of 292 patients with pelviureteric junction obstruction seen at the Mayo Clinic during a 10-year period, 10 were identified as having intermittent hydronephrosis. Of the various provocative methods used to stimulate

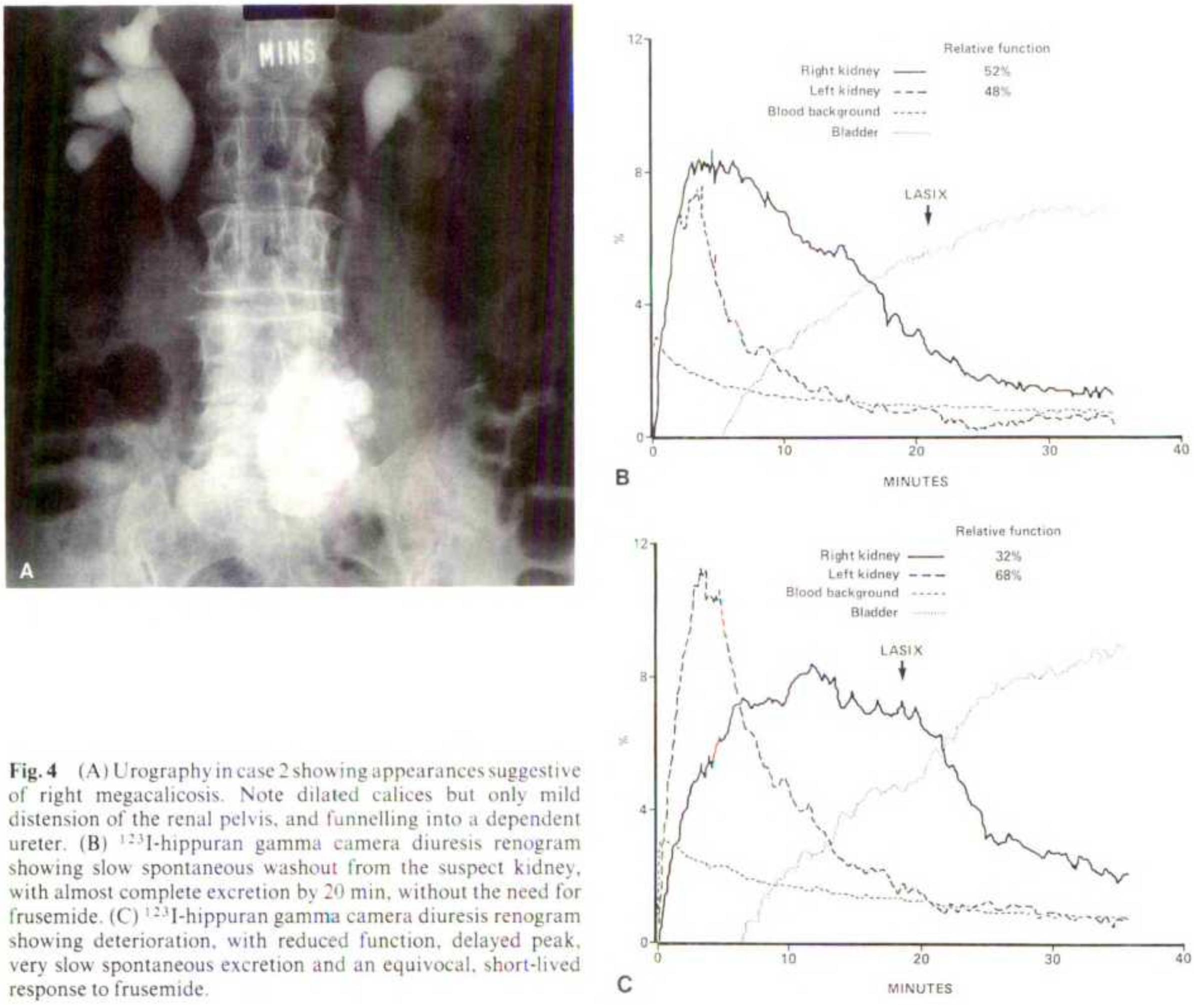

Fig. 4 (A) Urography in case 2 showing appearances suggestive of right megacalicosis. Note dilated calices but only mild distension of the renal pelvis, and funnelling into a dependent ureter. (B) ^{123}I-hippuran gamma camera diuresis renogram showing slow spontaneous washout from the suspect kidney, with almost complete excretion by 20 min, without the need for frusemide. (C) ^{123}I-hippuran gamma camera diuresis renogram showing deterioration, with reduced function, delayed peak, very slow spontaneous excretion and an equivocal, short-lived response to frusemide.

obstruction (Malek, 1983), diuretic urography was found to be the most useful. The 2 patients in this report were 2 of 62 consecutive cases of idiopathic hydronephrosis encountered during a 5-year period.

This report casts no doubt on the existence of primary megacalicosis as a non-obstructive cause of dilatation of the upper urinary tract but does suggest that between obstructive episodes, intermittent hydronephrosis may give radiological appearances very similar to those of primary megacalicosis. The clue may lie in the shape of the renal pelvis; in both cases reported here, the pelvis was thought to be distended but not significantly dilated. However, it was not completely normal, and in megacalicosis it usually is.

In conclusion, it is suggested that, between obstructive episodes, intermittent hydronephrosis may give radiological appearances misleadingly suggestive of non-obstructive primary megacalicosis. If either of these conditions is suspected, provocative testing will be required, including diuretic renography, maximal (F–15) diuresis renography (Upsdell *et al*., 1988), resting renal pelvic pressures or "unphysiological" (15–20 ml/min perfusion rates) perfusion pressure flow studies. Regular diuresis renograms with split function and drainage studies to monitor progress are recommended when the diagnosis remains uncertain, and arrangements for "acute-pain" IVUs in symptomatic cases are essential if intermittent hydronephrosis is not to be missed.

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Primary Endoscopic Surgery for Ureteric Stones

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Summary—A group of 184 consecutive patients requiring surgery for ureteric stones was studied over a 4-year period. The success rate for primary endoscopic management was 90.3%; 12 patients required ureterolithotomy for failed endoscopic manoeuvres and complications occurred in 5.5%. Optimum methods of treatment for ureteric stones according to size and location are suggested.

The introduction of extracorporeal shock wave lithotripsy (ESWL) has altered dramatically the management of patients with renal stones. Although ESWL can be used to treat ureteric stones (Miller *et al.*, 1985), the low availability of lithotriptors and poor success rates for ESWL monotherapy will result in the continued use of endourological procedures and ureterolithotomy for the treatment of patients with ureteric stones.

This report is an attempt to identify the optimum methods for treatment of ureteric stones.

Patients and Methods

The study group comprised 184 consecutive patients requiring surgery for ureteric stones seen over a 4-year period starting in March 1983: 185 primary procedures were carried out; this total included 1 patient with bilateral stones. The position of the stones is indicated in Table 1.

Since March 1983, primary endoscopic removal of ureteric stones has been attempted, provided that surgical intervention was indicated. The indications for surgery have not changed and endoscopic treatment was offered to patients if pain persisted for more than 48 h, or if the presence of stone and obstruction or infection coexisted. In addition, patients with stones >8 mm in diameter were offered endoscopic removal.

The procedures for stone removal and the site of the stones are shown in Table 2. There were 2 main methods of treatment. The short ureteroscope, with basketing of stones under vision or ultrasound disintegration (Tolley, 1987), was used primarily for the treatment of stones in the lower third of the ureter (Fig. 1). The ureteric orifice was first dilated under vision with a 4 F Fogarty balloon catheter, the balloon being distended with air to approximately 16 F diameter for 90 s. The catheter was advanced up the ureter and the ureteroscope

Table 1 Site of Ureteric Stones

Year	*Site* *Upper*	*Middle*	*Lower*	*Total*
1983	8	2	11	21
1984	9	8	12	29
1985	15	14	27	56
1986	18	12	37	67
1987	3	2	7	12
Total	53	38	94	185

Table 2 Primary Operations for Stone Removal

Procedure	*Site of stone in ureter* *Upper*	*Middle*	*Lower*
Antegrade basket	8	2	
Stone basket			5
Push–pull	41	22	2
Endoscopic ureterolithotomy			2
Ureteroscopy	4	8	66
Ureteroscopy and meatotomy		2	9
Ureterscopy and ultrasound		4	10
Total	53	38	94

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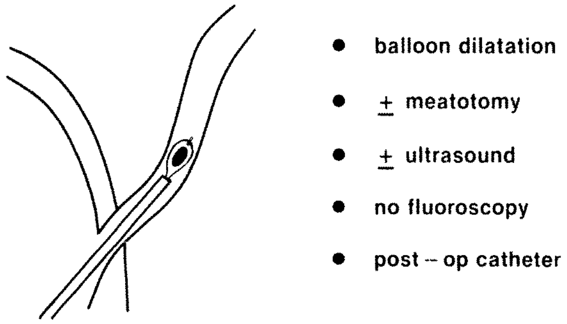

Fig. 1 Method of ureteroscopic stone extraction.

followed the line of the catheter until the vesicoureteric junction had been negotiated. (This procedure may require further dilatation of the ureter under vision.) After negotiating the intravesical ureter, the Fogarty balloon catheter was withdrawn and a 4 F Pfister-Schwarz stone basket was introduced through the operating channel of the ureteroscope and into the ureter. This basket was used as a guide to show the direction of the ureter. Once the stone was located the basket was negotiated beyond it and the stone engaged in the open basket under vision. Both stone and basket were then gently withdrawn. Stones >9 mm in diameter were fragmented by means of direct contact with the Storz ultrasound probe and fragments removed with grasping forceps. The ureter was then reinspected with the ureteroscope to check that there was no perforation and a 4 F ureteric catheter was inserted under vision and secured with the aid of a 16 F latex Foley catheter. The ureteric catheter was removed after 48 h.

Stones in the upper third of the ureter were pushed back into the kidney using an 8 F ureteric catheter passed via the cystoscope (Fig. 2). The stone's movement was monitored by fluoroscopic screening and it was nudged back gently by direct contact with the catheter if the collecting system was obstructed. In the event of this measure failing, the stone was flushed back with saline or dilute contrast. A lubricant was required occasionally and 2% lignocaine gel was mixed with normal saline for this purpose (in proportions 30:70) (Lupu *et al.*, 1986).

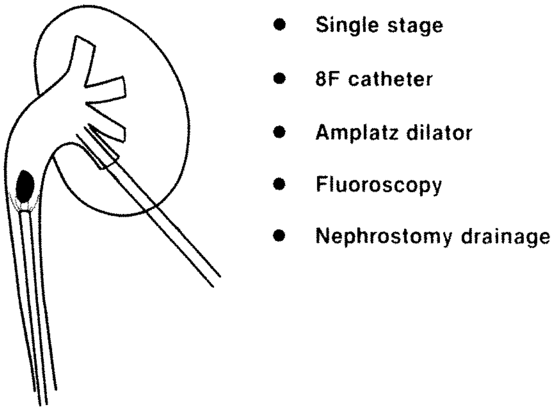

Fig. 2 "Push–pull" extraction.

A single-stage percutaneous nephrolithotomy was then performed under general anaesthesia with the patient lying in the prone position by the method described previously (Tolley and Buist, 1986).

Antegrade basketing of the stone through a percutaneous track in the lower pole was performed in 1983 but was abandoned because of the high radiation exposure to patients and staff.

Two patients with large impacted stones in the lower third of the ureter were treated by endoscopic ureterolithotomy. A ureteric catheter was placed in the ureter and a meatotomy performed with a Collin's knife. The incision was extended along the superomedial aspect of the ureter until the level of the stone was reached approximately 3 cm from the bladder. The stone was removed with the aid of grasping forceps and a 4.8 F silicone double-J stent was inserted through a short ureteroscope.

Results

The success rate of the procedure is summarised in Table 3. This has gradually increased to over 90% since a primary endoscopic approach to the management of ureteric stones was adopted in 1983. The overall success rate was 90.3% for primary endoscopic management. Failure of primary endoscopic management occurred in 19 patients, of whom 12 eventually required ureterolithotomy to render them stone-free (Table 3).

Table 3 Reasons for Failure

	Site of stone		
	Upper	*Middle*	*Lower*
No.	*5*	*9*	*5*
Size ≥9 mm	3	6	1
>1 stone	—	—	1
Fixed stone	4	3	—
Access		6	3
Obesity	2	4	
Non-dilated ureter	—	4	—

Complications were noted in 10 patients undergoing endoscopic procedures (5.5%) and in 1 patient undergoing open surgery for failed ureteroscopic stone extraction. Perforation of the ureter occurred in 4 cases. This was recognised at the time of operation in 2 cases and a double-J silicone stent inserted. Two patients developed post-operative pain and fever within 24 h of ureteroscopic extraction and ureteric perforation was diagnosed after emergency intravenous urography. Both of these patients were treated by percutaneous nephrostomy drainage. All 4 patients recovered uneventfully. Further minor episodes of pain and fever occurred in some patients and these may have been due to minor perforation of the ureter, especially at the level of the vesicoureteric junction. Post-operative pain was present in approximately 25% of patients, falling to less than 5% once per operative ureteric catheterisation became a routine procedure.

Three patients developed a ureteric stricture; 2 of these occurred after ureterolithotomy for failed ureteroscopic stone extraction early in the series and 1 patient developed a soft stricture in the distal ureter which was treated by endoscopic incision. Two other patients had persistent obstruction on IVU 3 months after the procedure and, at ureteroscopy, were found to have small stone fragments which were not demonstrated on the radiograph. The obstruction resolved after removal of the fragments in both cases. A prolonged ureteroscopy produced a deep vein thrombosis in 1 patient and another patient undergoing ureterolithotomy developed a superficial post-operative wound infection.

Discussion

It is clear that increasing experience of endoscopic techniques, combined with changes in instrument design, allows very high success rates to be achieved in patients where the primary method of management is endoscopic. However, the choice of method is less clear. In two-thirds of patients for whom endoscopic extraction has failed, the primary reason for failure has been the presence of a stone >9 mm in diameter. This is particularly true when there is an immobile stone in the middle third of the ureter which cannot be reached by antegrade or retrograde ureteroscopy. The availability of a ureteric ultrasound probe, and the ability to carry out endoscopic incision of the ureter, has resulted in fewer failures in the past 2 years. Stones in the middle third of the ureter remain the most difficult to reach and this is particularly so in obese patients or those with a non-dilated ureter. Failure to extract stones endoscopically from the middle third of the ureter was thus 5 times more likely to occur as failure to extract stones from the lower third in this series. Similarly, failure to remove stones in the upper third occurs more frequently than failure in the lower third of the ureter. In the absence of obstruction to the ureter, the ability to carry out retrograde ureteric manipulation is reduced and the presence of a large stone in a non-dilated upper two-thirds of the ureter should be regarded as a relative contraindication to stone extraction.

It remains to be seen what impact extracorporeal shock wave lithotripsy will have on the rapidly changing management of ureteric stones in the United Kingdom, but it should be noted that ESWL monotherapy (*i.e. in situ* treatment) for ureteric stones has a success rate of only 60% (Miller *et al.*, 1985). However, when combined with minimally invasive measures such as stent manipulation, the success rate rises to over 90% (Fuchs *et al.*, 1987). Although the procedure of push–pull may be replaced by retrograde manipulation of upper ureteric stones into the renal pelvis followed by lithotripsy (push–bang), ureteroscopic extraction of stones in the lower third of the ureter will remain the treatment of choice.

The largest problem area remains the middle third of the ureter, where localisation of stones by second generation lithotriptors using ultrasound is difficult or impossible and stones overlying a vertebral transverse process cannot be treated irrespective of the method of imaging. Attempted extraction by antegrade ureteroscopy or push–pull/bang may therefore remain the treatment of choice in this situation. Access to lithotripsy will alter the management of only a relatively small group of patients with high stones. When the reasons for failure of endoscopic extraction are studied (Table 3) and the fate of the stones is followed, certain guide lines regarding optimal therapy can be produced (Table 4): stones in the lower third are best managed by ureteroscopy alone, in combination with ultrasound disintegration if necessary. Stones in the upper ureter should be managed by retrograde ureteric manipulation and percutaneous extraction (push–pull) or EPL (push–bang) when available. Stones which cannot be manipulated should be extracted by antegrade ureteroscopy whenever possible.

For large stones in a non-dilated collecting system above the pelvic brim in the middle third of the ureter, an attempt at retrograde manipulation should be made; if this fails, ureterolithotomy is advised, particularly in the obese patient.

Table 4 Optimal Approaches to Ureteric Stones

	Obstruction		*Stone size*		
Site	*Present*	*Absent*	< 9 *mm*	> 9 *mm*	*Operation*
Upper	Yes		+	+	Push–pull
		Yes		+	Antegrade URS
		Yes	+		Antegrade URS ± retrograde manipulation
Middle	Yes		+	+	Push–pull
		Yes	+		URS
		Yes		+	URS + ultrasound/ureterolithotomy
Lower	Yes		+	+	URS ± ultrasound
		Yes	+	+	URS ± ultrasound

URS: Ureteroscopy.

Ureteroscopy will continue to have a fundamental role in treating ureteric stones, both for primary extraction and the removal of "steinstrasse" produced by lithotripsy. In the absence of ready access to ESWL, endoscopic management is the treatment of choice. An attempt at endoscopic extraction should be made in all cases, with ureterolithotomy reserved for patients in whom primary endoscopic management has failed.

Acknowledgement

The author thanks his many colleagues in South-East Scotland who have referred patients for stone management.

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Evaluation of Surgical Procedures for Bilharzial Strictures of the Ureter

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Summary—A series of 35 patients, with unilateral hydronephrosis complicating bilharzial stricture of either the upper or the middle third of the ureter, was divided into 2 groups. Group A, comprising 21 patients, was treated by resection anastomosis. Group B, comprising 14 patients, was treated by other reparative procedures without resection of the stricture. The results of the surgical correction, assessed clinically and radiologically, showed that significantly better results were achieved with resection anastomosis than with the other procedures.

Ureteric strictures are a common complication of urinary bilharziasis. There is general agreement that lower ureteric bilharzial strictures are best treated by vesicoureteric reimplantation (Omer *et al.*, 1975; Al Shukri and Alwan 1983), although claims of success with repeated endoscopic dilatation have been reported (Umebrah, 1981; Jacobsson *et al.*, 1987). However, the treatment of upper and middle ureteric strictures is open to debate. Problems in bridging ureteric defects following resection of long and multiple strictures encouraged urologists in endemic areas to devise alternatives. The aim of this report was to compare the results of resection anastomosis of strictures of the upper and middle third of the ureter with those of other plastic repairs where resection was not carried out.

Patients and Methods

The study group comprised 35 patients with unilateral bilharzial strictures of either the upper or the middle third of the ureter (22 left, 13 right) and a past history of urinary bilharziasis. There were 30 males and 5 females whose ages ranged from 20 to 65 years (mean 35.2). All underwent a full clinical assessment, urine analysis, blood urea and serum creatinine estimation and intravenous urography. The upper third of the ureter was involved in 19 cases and the middle third in 16. The pathological diagnosis of bilharziasis was established by histological examination of specimens obtained at surgery. The patients were divided into 2 groups according to the length of the ureteric stricture as measured intra-operatively.

Group A included 18 males and 3 females whose stricture was more than 1 cm in length; surgery consisted of resection of the diseased segment and oblique anastomosis by 3/0 chromic catgut interrupted stitches, with post-operative ureteric tube splintage. The distal normal ureter was split longitudinally in some cases to ensure even anastomosis to the dilated proximal ureter. In most cases the stricture was 1 to 2 cm long. However, in 1 patient a 5-cm stricture was resected and the gap bridged by direct anastomosis after mobilisation of the extremely tortuous ureter.

Group **B** comprised 14 patients (12 males and 2 females) with a stricture measuring less than 1 cm. They were treated either by Y-V plasty (8 cases) or by longitudinal incision of the stenosed segment with oblique closure (6). Ureterolysis of the proximal and distal ureter was added when indicated and the repaired ureter was tube splinted in all cases.

All patients were interviewed 2 months after surgery to assess renal pain and to collect urine for analysis and culture. IVU was also performed. Radiological regression of hydronephrosis and

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hydroureter, as judged by comparison with the contralateral side, was considered excellent when the pelvicaliceal system and ureters returned to normal (Fig. 1). It was regarded as moderate when dilatation improved but did not return to normal (Fig. 2) and poor if there was no regression (Fig. 3).

Statistical significance was assessed by Student's *t* test.

Results

Clinical presentation

All patients presented with renal pain and 2 patients in group A (9.5%) had a renal mass. Urine analysis revealed significant pyuria in all patients and microscopic haematuria in some. Bilharzial ova were seen in the urine of 4 patients (11%). Blood

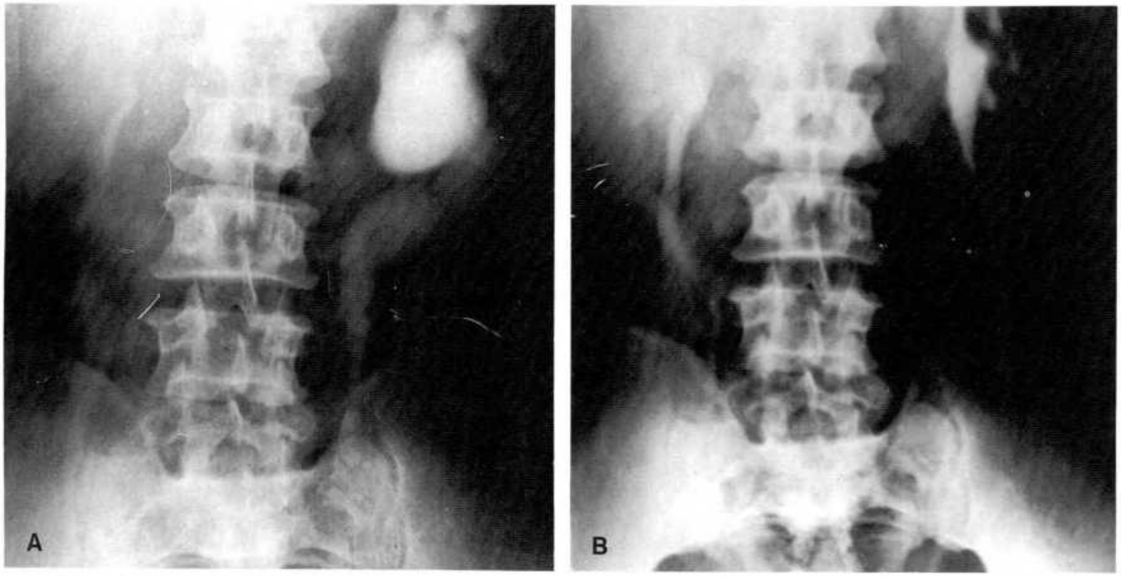

Fig. 1 (A) IVU showing marked left hydronephrosis in a Group B patient. (B) IVU in same patient 2 months after resection anastomosis showing excellent regression.

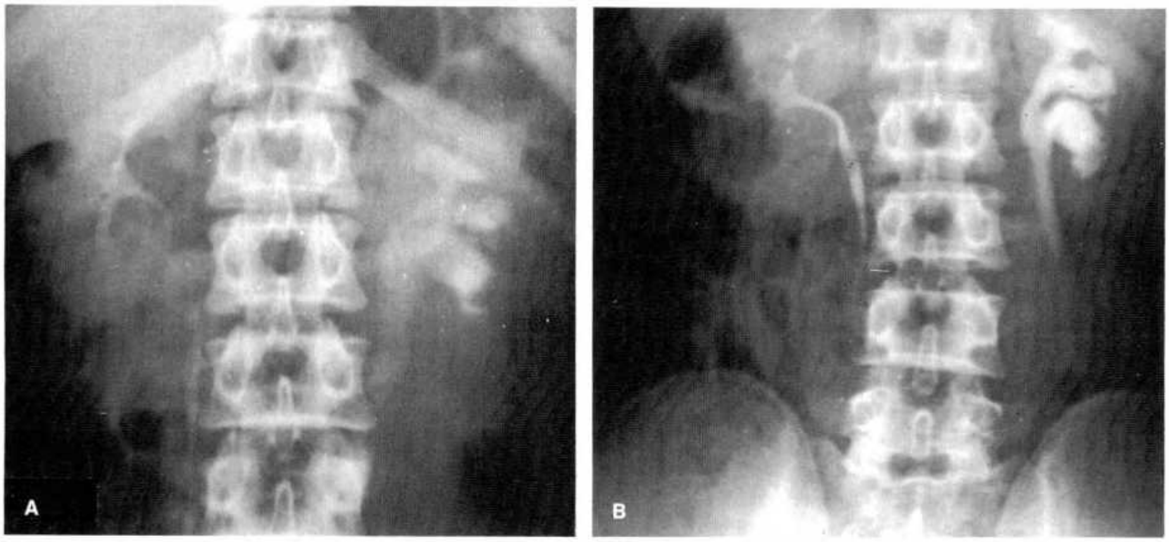

Fig. 2 (A) IVU showing left hydronephrosis in a Group B patient. (B) IVU in same patient 2 months after Y-V plasty showing moderate regression.

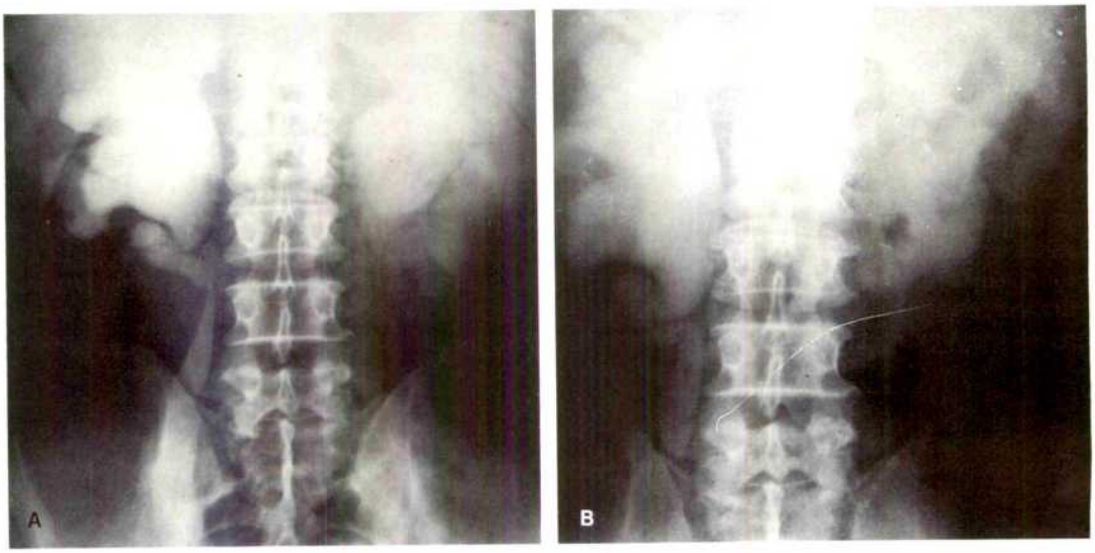

Fig. 3 (A) IVU showing right hydronephrosis in a Group B patient. (B) IVU in same patient 2 months after longitudinal incision with oblique closure of the stenosed segment in the mid-ureter: poor regression.

urea and serum creatinine were normal and urine culture grew a variety of organisms in all cases.

Post-operative clinical assessment and complications

Renal pain persisted in 2/21 patients (9.5%) in group A and 5/14 (36%) in group B ($P<0.01$). Significant pyuria with positive urine culture continued post-operatively in 2 group A patients (9.5%) and 5 of those in group B (36%) ($P<0.01$). Urinary leakage from the site of the repair occurred in 2 group B patients (14%) but in none of the group A patients. The leakage stopped after insertion of a ureteric catheter in 1 patient but revision was required in the other case.

Post-operative radiological assessment

Regression was excellent in 8 patients (38%) in group A compared with 1 (7%) in group B ($P<0.005$). It was moderate in 8 patients (38%) in group A, and 5 (36%) in group B ($P>0.05$) and poor in 5 patients (24%) in group A compared with 5 (36%) in group B ($P<0.05$). Hydronephrosis and hydroureter progressed in 3 patients (21%) in group B but in none of the group A patients.

Discussion

Urinary bilharziasis is an endemic parasitic disease in many countries of the Middle East. It involves mainly the urinary bladder and lower ureter, and less commonly the middle and upper ureter. Inadequate treatment, or reinfestation, eventually results in fibrosis and occasionally calcification, which may give rise to a localised stricture in the ureter. Failure of peristalsis occurs if a long ureteric segment is involved with replacement of the muscle layer by fibrous tissue, without necessarily encroaching on the lumen. Both complications lead to stasis and infection; thus the commonest presenting symptoms in our patients were loin pain and pyuria. The disease is usually bilateral but occasionally affects only 1 side. Patients with unilateral pathology were deliberately selected for this study to permit evaluation of the results of surgery in comparison with the unaffected contralateral collecting system.

Surgery of bilharzial ureteric strictures is a matter of controversy. Resection of the unhealthy fibrotic segment with an oblique end-to-end anastomosis has been described as the ideal treatment (Makar, 1955; Maged, 1971), despite the fact that resection is known to interrupt the continuity of the propulsive peristaltic wave which dies at the anastomosis. New waves start in the distal segment, however, as shown by electroureterographic and cineradiographic studies (Butcher and Sleator, 1956; Caine and Hermann, 1970). Temporary interruption of peristalsis by resection is acceptable when anastomosing a healthy ureter but is undesirable in the unhealthy bilharzial ureter where contractility is already weakened by fibrosis. Multiple bilharzial strictures, or involvement of a long segment by a fibrous stricture, preclude resection since the problem arises of bridging wide or multiple gaps. Alternative reparative procedures are therefore being sought for the treatment of bilharzial ureteric strictures. Umebrah (1981) advocated intermittent instrumental dilatation for bilharzial stricture of the ureter, although others have reported failure of repeated dilatation due to re-stenosis (Maged, 1977; Omer *et al.*, 1975; Al Shukri, 1983).

Fourteen patients in group B underwent correction of the stricture either by Y-V plasty (8 cases) or longitudinal incision with oblique closure (6). The clinical improvement, as judged by eradication of renal pain and infection, was significantly better with resection anastomosis than with the other procedures ($P<0.01$). Moreover, post-operative urinary leakage occurred in 2 group B patients but in none of those in group A who underwent resection.

Judging by radiological improvement, regression of hydronephrosis and hydroureter was excellent in 38% of patients in group A compared with only 7% in group B ($P<0.005$), moderate in 38% in group A and 36% in group B ($P>0.05$), mild in 24% in group A and 36% in group B ($P<0.05$). None of the patients in group A had post-operative progression of hydronephrosis, but 21% in group B showed this feature. Post-operative urographic studies support the advantages of resection anastomosis compared with other corrective surgical procedures. This is probably because resection removes the pathological fibrotic segment which in our patients demonstrated endarteritis obliterans on histological examination. Under these circumstances it is conceivable that plastic operations without resection are doomed to fail because of re-stenosis or urinary leakage, as occurred in 2 patients in group B (14%).

It was concluded that resection anastomosis for bilharzial ureteric stricture, if technically feasible, is superior to less extensive plastic surgery procedures where the diseased segment is not excised. Although resection might interrupt the ureteric peristaltic wave in the immediate post-operative period, new muscles replace the scar of the anastomosis if the latter connects 2 healthy ureteric ends.

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Adenocarcinoma of the Urinary Bladder

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Summary—We report 40 patients seen over a 15-year period with a histological diagnosis of adenocarcinoma of the bladder; 18 patients had primary adenocarcinoma of the bladder, arising either from the urachus or from glandular metaplasia of the urothelium, and the other 22 had secondary lesions representing invasion from adjacent structures, notably prostate, colon and ovary. In this latter group symptoms related to the primary lesion were variable. The distinction between primary and secondary neoplasm is an important one and was rarely made on the basis of endoscopic or clinical findings alone. Urachal tumours were more common in females, whereas primary and secondary vesical adenocarcinomas were more common in males. The urachal tumours also occurred in a younger age group. Most of the adenocarcinomas, urachal or primary, were already advanced at the time of diagnosis. All tumours were palpable bimanually after resection and were at least T2 or T3. In the urachal carcinomas the results of partial cystectomy were disappointing because of the high rate of local recurrence and death from metastases. Primary non-urachal vesical adenocarcinoma carried an even poorer prognosis if non-radical surgery was carried out. The mean survival was 13 months. Radiotherapy was not effective in urachal and primary adenocarcinomas as these tumours are generally radioresistant. The treatment of secondary adenocarcinoma was governed by the primary site of the tumour. Radical surgery combined with chemotherapy and radiotherapy appeared to give the longest survival in the colonic tumours. Patients with prostatic cancer had a poorer survival rate than those with the same stage tumour but without bladder involvement, with renal failure secondary to obstructive uropathy being the commonest cause of death.

Adenocarcinoma of the bladder is classified into 3 categories according to its origin: primary, urachal and metastatic (Wheeler and Hill, 1954). Primary adenocarcinoma of the bladder is an uncommon tumour, comprising only 0.5 to 2% of all primary urothelial tumours (Thomas *et al.*, 1971), but it is the most commonly reported malignancy of the exstrophic bladder. Carcinoma of the urachus is even more rare. Criteria for separating it from primary adenocarcinoma of the bladder are well established (Mostofi *et al.*, 1955). The histogenesis of the urachus is well documented (Begg, 1930) but the pathogenesis of urachal carcinoma is controversial. Metastatic adenocarcinoma in the bladder is usually a direct extension from a primary lesion in the colon, prostate or the female genital tract.

The present study comprised a retrospective analysis of 40 patients seen between 1972 and 1985. In all cases an initial histological diagnosis of adenocarcinoma was made on bladder biopsies. Subsequent investigations showed that 18 of these were primary tumours, of which 10 were urachal. The 22 patients with secondary tumours represented invasion from prostate, colon and ovary. Patients with areas of transitional cell carcinoma were excluded because they were considered to be examples of adenomatous metaplasia in transitional cell carcinoma and not true adenocarcinomas (Pugh, 1959).

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Patients and Methods

We studied the case notes of 40 patients who presented to the Royal Marsden and St Peter's Hospitals between 1972 and 1985 and in whom an initial diagnosis of adenocarcinoma was made on bladder biopsies. Each patient had been evaluated to establish the aetiology of the adenocarcinoma. This included a full urological investigation and a gastrointestinal or gynaecological investigation where the tumours were thought to be invading from a surrounding organ. Parameters studied were age, sex, symptoms, pathological findings, treatment and survival.

Results

After investigation, 18 patients were found to have primary adenocarcinomas of the bladder, 10 of which were urachal in origin. Of the 22 patients with secondary bladder tumours the primary tumours were from the colon, prostate and ovary. The age and sex distribution are shown in Table 1. Urachal tumours occurred more often in females, whereas primary and secondary vesical adenocarcinomas were commoner in males. The urachal tumours also occurred in a younger age group, the mean age being 49 years compared with 67 and 65 years in the primary and secondary adenocarcinoma groups respectively.

Haematuria, with or without irritative bladder symptoms, was the primary symptom in most of these patients (Table 2). In all of the patients with bladder secondaries the initial symptoms were related to the urinary tract. Intravenous urography was performed in all but 2 patients with bladder secondaries. Abnormalities were noted in all patients with primary non-urachal tumours but the findings were normal in 7 urachal and 15 secondary tumours (Table 3).

Cytological examination of the voided urine was performed in 21 patients. Atypical or malignant cells were noted in approximately half of the cases and these were equally distributed in the 3 groups.

The endoscopic features are shown in Table 4. Most primary tumours had a solid or ulcerating appearance on cystoscopy. It is important to note that 10 tumours that later proved to be secondary were described as papillary lesions. All of the tumours were palpable bimanually after resection and were at least T2 or T3. By definition, urachal tumours arise from the vault of the bladder and non-urachal primary tumours elsewhere. Secondary tumours were found anywhere in the bladder.

Table 1 Age and Sex Distribution

	Urachal (n=10)	*Primary (n=8)*	*Secondary (n=22)*
M F	3·7	6:2	15:7
Age (years)	29–70	46–89	50–80
(Mean)	(49)	(67)	(65)

Table 2 Presenting Symptoms

	Urachal (n=10)	*Primary (n=8)*	*Secondary (n=22)*
Painless haematuria	5	3	13
Bladder symptoms with haematuria	4	4	7
Bladder symptoms without haematuria	1	1	2

Table 3 Intravenous Urogram Findings

	Urachal (n=10)	*Primary (n=8)*	*Secondary (n=22)*
Upper tract dilatation	1	4	3
Vesical filling defect	2	5	6
Normal	7	0	15
Not done	1	0	1

Table 4 Endoscopic Findings

	Urachal (n=10)	*Primary (n=8)*	*Secondary (n=22)*
Appearance			
Solid/ulcerating	10	6	12
Papillary	0	2	10
Site			
Vault	10	0	3
Lateral	0	6	14
Base	0	2	5

Investigation of the secondary vesical adenocarcinomas showed the primary site to be the colon in 12 cases, prostate 8 and ovary 2. Of the colonic tumours invading the bladder 10 were rectosigmoid and 2 caecal in origin.

Figure 1 shows the various treatments used and their outcome in the urachal tumours; 9 of the 10 patients with urachal tumours were treated by partial cystectomy and 2 of them also received postoperative radiotherapy (DXT); 3 are alive and well but the follow-up of 2 patients does not extend beyond 3 years. One patient presented at 3 years with pulmonary metastases which were resected.

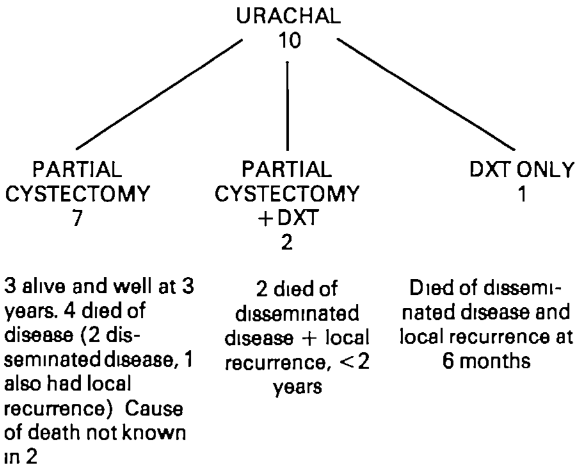
URACHAL
10
PARTIAL CYSTECTOMY
7
PARTIAL CYSTECTOMY
+DXT
2
DXT ONLY
1
3 alive and well at 3 years. 4 died of disease (2 disseminated disease, 1 also had local recurrence) Cause of death not known in 2
2 died of disseminated disease + local recurrence, <2 years
Died of disseminated disease and local recurrence at 6 months

Fig. 1 Results of treatment in patients with urachal carcinoma.

He has no evidence of disease 1 year later but has a very small capacity bladder secondary to the DXT and this is very slow to recover. Six patients are dead, of whom 4 died within 2 years of disseminated disease; 3 of the 4 also developed local recurrence. The cause of death in the remaining 2 is not known. The patient who received DXT alone died of his disease within 2 years.

Of the 8 patients with primary non-urachal tumours, 2 were treated with total cystectomy, including a patient with exstrophy. Both are alive and well at 2 and 3 years. The 1 patient treated by partial cystectomy, and all 5 treated by DXT alone, died within a year.

Figure 2 shows the outcome of the 12 patients with secondary tumours from the bowel; 3 had colonic resection and total cystectomy and are alive, well and without recurrent disease 1 to 3 years later; 9 patients had colonic resection and partial cystectomy and 5 of them died of disease within 18 months, including 1 post-operative death. One patient subsequently underwent total cystectomy for a local recurrence and is well at 2 years; 3 were lost to follow-up. Of the 2 patients with ovarian adenocarcinoma, 1 received DXT only and the other had a hysterosalpingoophorectomy with partial cystectomy. Both were lost to follow-up. All 8 patients with prostatic carcinoma were staged as T3/4 NX M1. One patient treated with DXT alone died of renal failure within 3 months. The other 7 were treated with hormonal manipulation; 5 died of disseminated disease within 18 months and 2 were lost to follow-up.

Discussion

When a histological examination of the bladder tumour discloses adenocarcinoma, the neoplasm has several possible diagnoses. It may represent primary metaplasia within a transitional cell carcinoma, a urachal carcinoma, a metastasis or an adenocarcinoma arising from metaplastic glandular epithelium of a normal or exstrophic bladder.

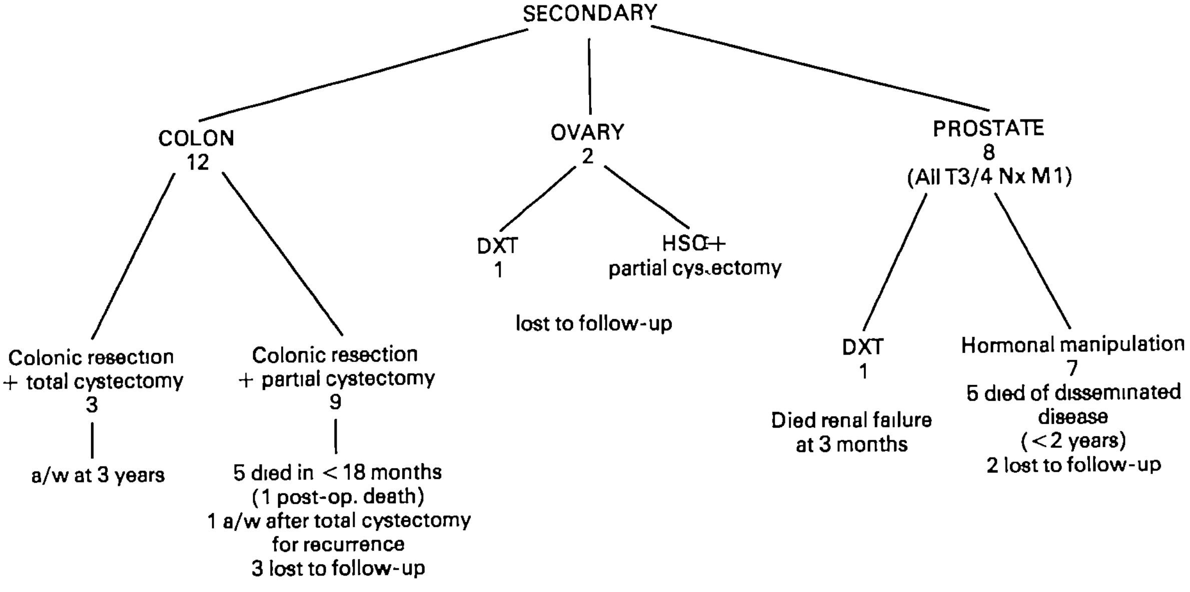

Fig. 2 Results of treatment in patients with secondary adenocarcinomas in the bladder

Adenocarcinoma of the bladder may be classified as primary, urachal or metastatic, based on the original site of the tumour. Transitional cell tumours with areas of glandular metaplasia are regarded as transitional cell carcinoma and are important in the histological differential diagnosis. Transitional epithelium retains the ability to transform by metaplasia into squamous or glandular epithelium. A primary vesical adenocarcinoma arises *de novo* from transitional epithelium that has undergone glandular metaplasia. These lesions result from metaplasia of epithelial cell nests of Von Brunn and may be enhanced by urinary infection. Several histological subtypes of primary adenocarcinoma have been described: glandular not otherwise specified, colonic type, signet ring cell and clear cell (mesonephric) type (Anderstrom *et al.*, 1983). The tumours may show a single histological pattern or any combination. Urachal adenocarcinoma is a tumour arising in the vault of the bladder in a patient in whom a primary tumour elsewhere cannot be found and where the adjacent urothelium does not exhibit glandular metaplasia. The tumour extends deep in the bladder wall, umbilicus, space of Retzius and may also infiltrate the anterior abdominal wall (Mostofi *et al.*, 1955). The tumours are mostly intramural with either an ulcerated or intact epithelium overlying the lesion. Urachal remnants may be connected to the tumour. The histogenesis of the urachus is well documented but opinions differ on the pathogenesis of urachal carcinoma. Embryonic inclusion of intestinal epithelium (L'Opez *et al.*, 1966), proliferation of the normal adenomatous structure in the intramucus part of the urachus (D'Alonzo, 1966) and metaplastic transformation of the urothelium (Allen and Henderson, 1965) have all been postulated as a possible pathogenesis of a urachal carcinoma. Metastatic adenocarcinoma usually occurs by direct infiltration from surrounding organs.

The incidence of primary adenocarcinoma ranges from 0.5 to 2% of all primary bladder tumours. However, it is the most commonly reported tumour in exstrophic bladders. Urachal carcinoma is even rarer and represents approximately 1 in 1400 bladder tumours (Beck *et al.*, 1970). Metastatic adenocarcinoma is the commonest of the 3 and usually represents a direct extension from adjacent gastrointestinal or female genital tract. The age and sex distribution of urachal and primary adenocarcinomas in this series is similar to that described by Bennet *et al.* (1984) and Thomas *et al.* (1971). Urachal carcinomas occur in younger patients (mean age 49 years in this series). Haematuria, with or without bladder symptoms, appears to be the main presenting symptom in all reported series. However, it is interesting to note that in our patients with bladder secondaries the initial symptoms were also related to the urinary tract. This is at variance with other retrospective series (Mostofi *et al.*, 1955) and indeed with the not uncommon finding at operation of rectosigmoid tumour invasion of the bladder. This reflects the fact that such patients had been referred to specialist urological units. Had they presented with bowel symptoms, for example, they would have been sent elsewhere.

Most adenocarcinomas, urachal or primary, are already advanced at the time of diagnosis, which in the case of the urachus can be explained by its location in the bladder vault. In the present study, all tumours were stage T2 or T3 at the time of initial diagnosis. Anderstrom *et al.* (1983) noted that 64% of their tumours penetrated the muscular wall at the time of diagnosis regardless of the primary tumour location. Most of our patients were treated by surgery. Urachal tumours were treated by partial cystectomy with excision of the umbilicus. The survival in this group was only 44% at 2 years. Whitehead and Tessler (1971) reported a 25% 5-year survival rate with partial cystectomy and *en bloc* excision of the umbilicus. However, Kakizoe *et al.* (1983) reported better survival in patients treated with extended radical cystectomy with *en bloc* excision of the umbilicus. This is perhaps due to the histological evidence of wide and deep infiltration of the muscular layer of the bladder with an intact mucosa as well as nodal involvement. Three patients in our series had local recurrence after partial cystectomy. This may have been due to inadequate excision of the tumour and frozen section of the excised margins at the time of surgery is therefore advisable. Radiotherapy was not effective and is generally accepted to be of little value in this disease because adenocarcinomas are generally radioresistant. However, long-term survival with radiotherapy has been reported by Grogono and Shepheard (1969) and Thomas *et al.* (1971). There are few reports of patients treated by chemotherapy. Kakizoe *et al.* (1983) reported 1 patient treated with ifosfamide, nysmustine hydrochloride and dacarbazine with prolonged survival. Logothetis *et al.* (1985) reported that this tumour was sensitive to 5-fluorouracil. No series is sufficiently large for a definite conclusion to be drawn about treatment. The results of partial cystectomy are disappointing because of the high rate of local recurrence and death from metastases. Better results might be obtained by radical cystectomy, possibly with adjuvant 5-fluorouracil. Now that continent diversion can be offered to this relatively young group of patients, radical treatment becomes more attractive.

Primary non-urachal adenocarcinoma of the bladder carries an even poorer prognosis if non-radical surgery is carried out. The mean survival in this series was 13 months and similar observations have been made by Jones (1980). However, the survival rate following radical surgery for primary adenocarcinoma is much better. Malek *et al.* (1983) noted 80% and Jones *et al.* (1980) 100% 5-year survival rates with radical surgery. The site of these tumours, the most usual being the base and the lateral walls, appears to be a major factor contributing to this survival. Radical cystectomy thus appears to be the treatment of choice for non-urachal adenocarcinoma and this has also been observed by Bennet *et al.* (1984), Mostofi *et al.* (1955), Thomas *et al.* (1971), Jones *et al.* (1980) and Malek *et al.* (1983). Transurethral resection is of diagnostic and palliative value only.

The treatment of secondary adenocarcinoma is governed by the primary site of the tumour. Radical surgery combined with chemotherapy and radiation appears to give the longest survival in colonic tumours. Survival of the patients with prostatic cancer was poorer than that of patients with the same stage tumour but without bladder involvement. Renal failure secondary to obstructive uropathy was the cause of death in 4 of the 8 patients.

Diagnosis initially rests with the department of histopathology in the discovery that the lesion within the bladder is in fact an adenocarcinoma rather than a transitional cell tumour. Some clue as to its origin may arise from the microscopic finding of both the tumour and the adjacent urothelium. However, the distinction between primary, urachal and secondary tumour is largely a clinical one depending on the site of the tumour within the bladder and demonstrable absence or presence of a primary elsewhere. Many of these tumours are well advanced at the time of presentation and inevitably carry a poor prognosis. This may be due to the aggressive nature of the tumour because two-thirds are poorly differentiated and deeply invasive at the time of diagnosis.

In this small series the best results were obtained with radical rather than conservative surgery. Radiotherapy appears to offer little benefit but the role of post-operative chemotherapy requires further study.

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Conservative Treatment of Diffuse Carcinoma *in situ* of the Bladder with Repeated Courses of Intravesical Therapy

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Summary—We present a series of 13 patients with diffuse carcinoma *in situ* (CIS) of the bladder who failed an initial induction course of intravesical therapy with Mitomycin C, thiotepa, doxorubicin or Bacillus Calmette Guérin (BCG). Cystectomy, although indicated, was, for various reasons, not performed after the first failure of intravesical therapy and all patients were subsequently treated topically with the same or different agents. Of the 7 patients treated with 2 induction courses, 6 showed a complete response during a follow-up period of 24 to 42 months. Although 1 patient initially responded completely, he developed invasive transitional cell carcinoma (TCC) Grade IV 30 months later. Among the 3 patients who underwent 3 induction courses, 2 had a complete response at 42 and 60 months of follow-up and 1 developed TCC Grade IV with muscle invasion 18 months later. Two of the 3 patients treated with 4 induction courses are free of disease at 48 and 57 months; the third developed low grade, low stage TCC. This experience suggests that the majority of patients with CIS who fail initial treatment usually respond to further treatment with the same or a different drug. The question as to whether a second course of intravesical therapy, subsequent to failure of the first course, should be given before cystectomy requires further investigation.

The invasive potential of carcinoma *in situ* of the bladder is now well established (Daly, 1976; Farrow *et al.*, 1977). Among the patients with CIS, 42 to 83% will develop invasive cancer within a 5-year period (Althausen and Prout, 1976; Daly, 1976; Starklint *et al.*, 1976). While radical cystectomy is the accepted treatment, a trial of intravesical therapy is currently recommended for most patients. Failure to respond usually indicates the need for cystectomy (Soloway, 1980), although many patients respond to other agents. The extent to which successive intravesical agents can be safely employed, however, is unknown and fear of invasion and metastases prompts early aggressive therapy.

We present the results from a group of patients with diffuse CIS of the bladder who failed initial intravesical therapy and in whom cystectomy, although indicated, was not performed for various reasons. All patients were treated by further topical therapy with different agents until control of the CIS was achieved or until other indications for cystectomy were manifested.

Patients and Methods

Included in the study were 13 patients with diffuse CIS of the bladder, diagnosed between 1979 and 1985, for whom radical cystectomy was either contraindicated or rejected. All patients initially underwent an induction course of weekly treatments with 1 of the following drugs for 6 to 8 weeks: thiotepa (30–60 mg), Mitomycin C (20–40 mg), doxorubicin (30–60 mg), or Bacillus Calmette Guérin (BCG-Tice strain, 1 ampoule containing 5–6×10^8 colony-forming units). Some patients who responded to the induction course with Mitomycin

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C or BCG were further treated with a monthly maintenance dose. Whenever failure of 1 agent was noted, the drug was discontinued and a course of another drug was given. In some patients who responded initially to the first course but failed therafter, or who had a partial response, a second course with the same drug was given. Thus each patient was treated by successive instillations of 2 to 4 induction courses during the period of follow-up. Patients with persistent or recurrent positive urine cytology and/or positive bladder biopsies subsequent to the intravesical therapy were considered treatment failures. Response was judged complete when both urine cytology and bladder biopsies became negative after the intravesical therapy. All patients were followed by urine cytology and cystoscopy every 3 months and by bladder biopsies every 3 to 6 months.

Table 1 Clinical data

Patient no	*Age (years)*	*Irritative symptoms*	*History of TCC*
1	61	+	—
2	78	+	—
3	72	+	TCC grade 1–2 (0 months)
4	79	−	TCC grade 1–2 (2 years)
5	70	+	TCC grade 1–2 (2, 3 years)
6	66	+	—
7	58	−	TCC grade 1–2 (6 months)
8	66	+	—
9	56	+	—
10	70	+	—
11	70	−	TCC grade 1–2 (0 months)
12	79	+	—
13	74	−	TCC grade 1–2 (1, 4 years)

Results

All patients in the study were men (mean age 69 years, range 56–79). In 9 patients the presenting symptoms were frequency, urgency and dysuria; in 3 others CIS was found incidentally on random biopsies during follow-up cystoscopies and 1 patient presented with macroscopic haematuria (Table 1). Seven patients had CIS without a previous history of papillary transitional cell carcinoma, 4 had a previous history of low grade (1–2) low stage (O–A) bladder tumours which were resected 6 months to 4 years prior to CIS diagnosis. Two patients had low grade, low stage TCC at the time of diagnosis which were resected completely.

Of the 13 patients, 7 underwent 2 induction courses of topical chemotherapy, 3 had 3 courses and another 3 underwent 4 courses. Among 7 patients who were treated with 2 induction courses, 4 were treated initially with Mitomycin C, 2 with BCG and 1 with thiotepa (Table 2). These patients were treated subsequently with BCG (patients 1–6) and Mitomycin C (patient 7). Six patients showed a complete response during a follow-up period of 24 to 48 months. Patient no. 2, in whom cystectomy had been contraindicated because of his severe coronary heart disease, initially had a complete response but subsequently developed papillary TCC Grade IV 30 months later. The 3 patients who underwent 3 induction courses (Table 3, patients

Table 2 Duration and Results of Treatment in Patients treated with 2 Induction Courses of Intravesical Therapy

			Post-treatment		
Patient no	*Treatment*	*Duration of treatment (months)*	*Cytology*	*Biopsy*	*Months of follow-up (result)*
1	Mitomycin C	2	+	+	
	BCG	21	−	−	42 (CR)†
2	Thiotepa	1 5	+	+	
	BCG	12	− (30)*	− (30)*	30 (TCC)
3	BCG	2	−	+	
	BCG	12	−	−	24 (CR)
4	Mitomycin C	4	+	+	
	BCG	12	−	−	48 (CR)
5	Mitomycin C	2	+	+	
	BCG	24	−	−	32 (CR)
6	Mitomycin C	2	+	−	
	BCG	14	−	−	33 (CR)
7	BCG	1 5	+	−	
	Mitomycin C	11	−	−	36 (CR)

* Duration of response (months).

† Complete response

Table 3 Duration and Results of Treatment in Patients treated with 3 and 4 Induction Courses of Intravesical Therapy

Patient no	*Treatment*	*Duration of treatment (months)*	*Post-treatment*		*Months of follow-up (result)*
			Cytology	*Biopsy*	
8	Thiotepa	2	+	+	
	Mitomycin C	1.5	−	+	
	BCG	38	−	−	60 (CR)†
9	Thiotepa	2	+	+	
	BCG	2	+	−	
	BCG	2	−	−	42 (CR)
10	BCG	2	+	+	
	Mitomycin C	2	+	+	18 (TCC)
	Mitomycin C	2	+	+	Cystectomy
11	Mitomycin C	2	− (5*)	− (5*)	
	Mitomycin C	1	+	+	
	BCG	14	− (14*)	− (14*)	
	Doxorubicin	6	−	−	48 (CR)
12	Mitomycin C	2.5	− (12*)	− (12*)	
	Mitomycin C	1.5	+	+	
	BCG	2	+	+	
	Doxorubicin	2	−	−	57 (CR)
13	Thiotepa	1.5	+	+	
	Doxorubicin	1.5	+	+	
	BCG	2	− (6*)	− (6*)	
	Mitomycin C	1.5	−	−	60 (TCC)

* Duration of response (months)
† Complete response.

8–10) were followed up for 18 to 60 months. Although patient no. 8 failed treatment with thiotepa and Mitomycin C and patient no. 9 failed thiotepa and 1 course of BCG, both responded finally to BCG. The third (patient 10) developed bladder tumour after the failure of 1 course of BCG and 2 courses of Mitomycin C and then underwent cystectomy. In this patient, both urine cytology and bladder biopsies remained positive during and after the courses of treatment. Histological examination of the bladder showed papillary TCC Grade IV with muscle invasion but no lymph node metastases. Of the 3 patients who were treated with 4 induction courses (patients 11–13), 2 failed 2 induction courses of Mitomycin C and 1 course of BCG and finally responded to doxorubicin (patients 11 and 12). Both initially had complete responses to the first course of Mitomycin C (5 and 12 months respectively) and 1 (patient 11) responded also to BCG for 14 months. Another (patient 13) failed treatment with thiotepa and doxorubicin, failed after a 6-month response to BCG, then finally responded to Mitomycin C.

Discussion

Numerous studies support the concept that invasive bladder cancer represents an evolution from CIS (Daly, 1976; Farrow *et al.*, 1977). Starklint *et al.* (1976) showed that 23 of 43 patients developed invasive cancer during a follow-up period of less than 1 year. Althausen *et al.* (1976) noted that 10 of 12 patients with CIS developed invasive cancer during a follow-up period of 18 months. The latency period prior to invasion is currently unpredictable and there is no way of detecting those patients in whom invasion will occur before surgery. Cystectomy for diffuse CIS of the bladder is therefore recommended in numerous studies, most of which suggest a short trial of intravesical therapy followed by early cystectomy for patients whose CIS is not completely reversed (Soloway, 1980).

The results in the present study were obtained from a selected group in whom cystectomy was either contraindicated or rejected. Thus intravesical therapy was the only treatment available and was continued for a long period of time. Of the 13 patients included in the study, 10 have been free of tumour for 24 to 60 months; another patient developed low grade, low stage tumour. Of the 2 patients who developed invasive cancer, 1 had persistently positive cytology and histology and finally consented to cystectomy. These results indicate that CIS, which was initially resistant to one drug or recurred following an initial response, responded in most cases to further topical therapy. Jakse *et al.* (1984) showed that 10 patients with CIS had remission after topical therapy with doxorubicin for 24 months. Of the 10 patients, 3 had recurrence, all of whom achieved complete response after retreatment with doxorubicin. Prout *et al.* (1982) demonstrated that 5 of 16 patients with superficial bladder cancer (including CIS) who failed initial treatment with thiotepa subsequently responded to Mitomycin C. With the increasing number of effective drugs currently available for CIS, the question that remains is whether treatment failure after the instillation of 1 agent should remain an absolute indication for immediate cystectomy or whether another course with the same or a different agent should be given prior to surgery. The prognosis for patients who do not respond to topical therapy and have persistently positive cytology is poor; most develop invasive cancer or distant metastases. This occurred in 1 patient in our series who developed invasive TCC without distant metastases (patient 10). Droller and Walsh (1985) presented a series of patients with CIS who were treated with intravesical instillation of thiotepa. All had persistently positive urine cytology during treatment and 7 underwent cystectomy. On histological examination, 3 patients had positive lymph nodes and 4 died of distant metastases.

Although the present study was not conducted primarily to determine the efficacy of intravesical therapy with consecutive agents, the results suggest that initial failure of topical therapy in patients with CIS may not be an absolute indication for cystectomy. Most will respond to further topical therapy and may remain free of disease for long periods of time. However, any adoption of conservative treatment of this lethal disease must be approached cautiously. Radical cystectomy is still the safest therapy, since the presence of microscopic invasion often cannot be detected by biopsies. Riddle *et al.* (1976) showed that the best results for patients with diffuse CIS were achieved with radial cystectomy. Of the 12 patients treated with radical surgery, 7 remained free of disease 1 to 6½ years after surgery, whereas only 1 patient of the 11 who were treated with irradiation therapy remained alive. At the present time, we recommend immediate cystectomy for CIS patients with irritative symptoms and those with a history of high grade or invasive tumours. Other CIS patients are treated with an 8-week course of BCG. If they have a complete response they are given monthly maintenance for 1 year and monitored closely. Those who have either a partial response or no response are changed to Mitomycin C for a single 8-week induction course. Patients who still have not had a complete response undergo cystectomy. Further investigation of this approach is required to determine its efficacy and outcome in patients with CIS of the bladder.

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Is the Investigation of Most Stress Incontinence Really Necessary?

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Summary—The case histories of 494 women referred to a urodynamic clinic with the symptom of stress incontinence were studied. None had undergone previous incontinence surgery. In only 12 patients was stress incontinence the sole symptom. In the remainder, symptoms suggestive of detrusor instability were present in 417, of a voiding disorder in 261 and of an inflammatory disorder in 166. The sign of stress incontinence was present in only 168 patients and was not a reliable guide to the diagnosis of genuine stress incontinence. Urodynamic studies were necessary in 488 patients in order to obtain an accurate diagnosis.

The argument is still used that it is appropriate to diagnose genuine stress incontinence (GSI) if a woman complains only of stress incontinence and if stress incontinence can be demonstrated on clinical examination. This clinical diagnosis often precedes a decision to undertake surgical treatment of the stress incontinence. Urodynamic investigations are deemed unnecessary unless the patient has had previous surgery for urinary incontinence. This study sought to determine how often this argument was correct.

Patients and Methods

The computerised records of 873 consecutive female patients referred to a urodynamic clinic were analysed. This unit acts as both a primary and secondary referral centre. During the period of the study 36% of referrals came directly from General Practitioners and 64% came from other gynaecologists. Those patients who had undergone previous surgery for urinary incontinence were excluded from further study, in order to single out a group which would match patients referred to a non-specialist unit. The remaining 574 patients were questioned specifically about stress incontinence: 80 denied having the symptom; the remaining 494 patients who did complain of stress incontinence formed the study group.

After a full history and examination, all patients were examined with a full bladder and tested for the sign of stress incontinence. A mid-stream urine specimen was examined bacteriologically. Urine loss was quantified using a 2-h pad weighing test (Sutherst *et al.*, 1981). Urine flow rate and residual urine volume were measured. Urodynamic testing included supine and provocative subtraction cystometry, urethral pressure measurements at rest and during stress and detrusor voiding pressure. All definitions and units conform with the standards proposed by the International Continence Society (1976, 1977) except where specifically noted.

All data were stored on computer database and subsequently analysed to determine the incidence of patients with the sole symptom of stress incontinence, the sign of stress incontinence and a final diagnosis of genuine stress incontinence. The symptoms of patients with other relevant urinary symptomatology were analysed for their association with specific urodynamic diagnoses.

Results

Twelve of the 494 patients (2%) had stress incontinence as their only symptom; 482 (98%) had other symptoms as well; 417 (84%) had either urgency or urge incontinence; 261 (53%) had at least 2 of the

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following voiding symptoms: hesitancy, poor stream, sense of incomplete emptying, need to revoid immediately; 166 (34%) had either dysuria or other pain associated with micturition. Other common symptoms included frequency (10 or more times per day), nocturia (more than once per night), "no warning" leaks and enuresis.

The sign of stress incontinence at the initial clinical examination was present in 168 patients (34%). Six patients (1%) with stress incontinence as their only symptom also had the sign of stress incontinence and a final diagnosis of genuine stress incontinence.

The Table shows the final urodynamic diagnoses in patients who, in addition to the symptom of stress incontinence, had symptoms suggestive of detrusor instability (DI), symptoms suggestive of a voiding disorder and the sign of stress incontinence.

Discussion

Farrar *et al.* (1975) found that patients who complained of stress incontinence in the absence of any other micturition symptoms usually had stable bladders and did not require urodynamic investigation. We have shown that the symptom of stress incontinence by itself is very uncommon, even in patients who have not had previous incontinence surgery. Byrne *et al.* (1987) presented urodynamic data from 61 such patients. From our experience, over 4000 urodynamic studies would have been needed to find a study group of this size.

We did identify a small group of 6 patients where the original argument was found to be correct, *i.e.* an accurate clinical diagnosis of GSI would have been possible without urodynamics. These patients all complained only of stress incontinence, stress incontinence was demonstrated on clinical examination and the final urodynamic diagnosis was GSI alone. However, 488 of the 494 patients (99%) required urodynamic investigations before the diagnosis was clear: 482 (98%) had multiple symptoms; of the remaining 6 patients (1%), all of whom had the sole symptom of stress incontinence without the accompanying sign of stress incontinence, 1 had a diagnosis other than GSI alone.

The treatment of DI is usually non-surgical and because the fault lies in the detrusor rather than at the bladder neck, conventional bladder neck surgery cannot be expected to be of benefit. In a series of 73 patients with the symptom of stress incontinence, Jarvis *et al.* (1980) found that either urgency or urge incontinence was present in 51 (70%). Most patients in the present study had symptoms suggesting DI and needed urodynamic investigation to exclude this. Of the 494 patients complaining of stress incontinence, 417 had either urgency (81%) or urge incontinence (75%). Of these, 102 (25%) demonstrated detrusor instability during cystometry.

Table Symptoms and Signs and Final Diagnosis in 494 Patients Complaining of Stress Incontinence

Final diagnosis (n=494)	*SI+urgency or urge incontinence (n=417)*	*SI+2 voiding symptoms (n=261)*	*Sign of SI (n=168)*
GSI (n=290)	235	151	114
(59%)	(56%)	(58%)	(68%)
DI (n=46)	45	22	7
(9%)	(11%)	(8%)	(4%)
Mixed GSI/DI			
(n=60)	57	34	24
(12%)	(14%)	(13%)	(14%)
Mixed GSI/(inflammatory voiding or sensory problem			
(n=48)	37	29	23
(10%)	(9%)	(11%)	(14%)
Pure inflammatory, voiding or sensory problem			
(n=23)	18	10	0
(5%)	(4%)	(4%)	(0%)
Normal studies			
(n=27)	25	15	0
(6%)	(6%)	(6%)	(0%)

SI = symptom of stress incontinence GSI = genuine stress incontinence DI = detrusor instability Percentages in the final diagnosis column refer to the total study group

Flow disorders are unusual in women (Farrar and Osborne, 1984) but it is important that they be detected to avoid the occurrence of permanent urinary retention post-operatively. Now that efficient operations (*e.g.* colposuspension) are being used to restore bladder neck competence, it is even more important to identify normal detrusor function preoperatively; 261 patients (53%) had at least 2 symptoms suggestive of a detrusor voiding/outlet obstruction problem as well as stress incontinence. Of these, 60 (12% of the patients studied) had an abnormality of bladder emptying during urodynamics. During the study, such an abnormality was defined as a peak urine flow rate under 15 ml/s or a residual urine volume consistently over 50 ml.

Patients with symptoms suggestive of an inflammatory problem in the lower urinary tract may need further investigation such as cysto-urethroscopy and intravenous urography to exclude other pathology; 166 patients (34%) came into this category. The same symptoms may also be present in other conditions of lower urinary tract dysfunction.

The demonstration of stress incontinence on clinical examination was an unreliable guide to the diagnosis of GSI. It was present in only 161 (41%) of the 398 patients with the final diagnosis of GSI, either alone or mixed. Furthermore, 54 patients (32%) with this sign had a diagnosis other than GSI alone.

The human and financial costs of inappropriate surgery are considerable. It is time to rethink the dictum that "it is clearly impracticable to have all female patients with disorders of micturition undergo sophisticated pressure flow studies" (Farrar *et al.*, 1975). Since it is so uncommon to find a woman in whom it is possible to diagnose GSI correctly on purely clinical criteria, all women should undergo urodynamic investigation before surgery. This can happen only with the increasing development of urodynamic clinics and facilities.

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Ambulatory Monitoring of Bladder Pressures in Patients with Low Compliance as a Result of Neurogenic Bladder Dysfunction

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Summary—A group of 28 patients with neurogenic bladder dysfunction and low bladder compliance was studied using medium fill cystometry (CMG) and ambulatory monitoring (AM) during natural bladder filling. The aims of the study were to compare the 2 techniques and to determine if ambulatory monitoring might be useful in predicting upper tract dilatation.

AM demonstrated significantly lower end filling pressures compared with CMG. Phasic detrusor contractions were found more commonly during AM and the frequency of phasic detrusor contractions during AM was associated significantly with poor compliance identified during CMG.

Patients with upper tract dilatation had significantly greater residual urine volumes, higher pressure rises during CMG and higher frequencies of phasic detrusor contractions compared with those patients with normal upper tracts.

The high pressures seen at the end of a medium fill CMG were not found during AM and therefore are unlikely to be the underlying explanation of upper tract dilatation in such patients.

Whilst developments such as clean intermittent self-catheterisation, augmentation cystoplasty and artificial sphincters have helped to improve the quality of life of patients with injury to the spinal cord, the pelvic nerves or with myelodysplasia, the urological complications still contribute significantly to the morbidity of such patients (Donelly *et al.*, 1972; Gershon and O'Flynn, 1980).

In particular, renal failure secondary to upper tract dilatation remains a significant cause of morbidity. Several urodynamic factors have been described which may predict the development of upper tract dilatation, but the underlying mechanism remains obscure. These factors include high post-micturition residual urine volumes, low compliance during bladder filling and severe detrusor hyper-reflexia, particularly if accompanied by detrusor sphincter dyssynergia (McGuire *et al.*, 1981, 1983; Mundy *et al.*, 1982).

The use of an ambulatory monitoring system in the investigation of men with upper tract dilatation secondary to chronic retention of urine caused by bladder outflow obstruction has been reported previously from this department (Styles *et al.*, 1986, 1987). The poor detrusor compliance which was found during medium fill cystometry was not found during natural filling of the bladder. Moreover, previously unreported phasic activity was observed during natural filling, the frequency of which correlated well both with the presence of upper tract dilatation and with poor compliance found during CMG.

In view of these findings we carried out a study of patients with neurological bladder dysfunction to compare the results of medium fill urodynamic studies (CMG) with ambulatory monitoring of bladder pressures during natural filling (AM).

Patients and Methods

The series included 28 patients (20 men and 8 women; mean age 40 ± 22 years; range 15–74). The

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underlying neurological diagnoses were: sacral agenesis/spina bifida (14), post-abdominoperineal resection of rectum and anus (8) and spinal cord compression (6). Patients were recruited to the study as they presented to the urology department or as they were being assessed prior to a change in urological management. At the time of the study 19 were voiding *per urethram*, 6 were using clean intermittent self-catheterisation and the remaining 3 were managed by permanent indwelling catheter.

The criterion for entry to the study was low compliance on a conventional filling cystometrogram, defined as a tonic pressure rise greater than 25 cm H_2O at a filling rate of 100 ml/min excluding any superimposed hyper-reflexic contractions. The upper urinary tracts were assessed by an intravenous urogram or isotope renography (dilatation was recorded as present or absent).

Conventional pressure flow studies were performed using 4F fluid filled lines to measure rectal and bladder pressures, with zero reference being at the level of the symphysis pubis. A 10F catheter was used to fill the bladder at rates of 100 ml/min and 20 ml/min. Subtracted detrusor pressures were measured with the patient lying supine and the bladder was filled without draining any residual urine (Thomas *et al.*, 1975).

The end filling detrusor pressure and filling volume were measured, allowing calculation of compliance. During filling, the presence of detrusor hyper-reflexia (phasic contractions >15 cm H_2O) was recorded. Unless otherwise stated, the definitions of the International Continence Society were used (ICS, 1987).

The method of ambulatory monitoring has been described in full by Griffiths *et al.* (1987). Two microtip transducers were used to record intravesical and intrarectal pressures. The signals were amplified, sampled at 1 Hz and stored in a solid state memory with a 6-h capacity. The equipment was carried by the patient on a shoulder strap. After the study was complete the data were downloaded into a computer prior to printing a hard copy.

Detrusor pressure was measured continuously after a void or following self-catheterisation at the start of natural filling and again at the end of filling; these pressures were taken for analysis. On average, 3 voiding cycles were recorded during each investigation (3.1 ± 0.4) and mean values are reported for each parameter measured during the study. The presence of phasic bladder contractions greater than 15 cm H_2O was noted and their amplitude, frequency and duration were measured. These characteristics were combined into a single figure by measuring the area under the curve of subtracted detrusor pressure for 20 min prior to a void. This figure is referred to subsequently as A20.

A frequency/volume voided chart was completed by the patient during ambulatory monitoring and the filling volume was estimated from the volume voided, the amount of urine leaked during the study and ultrasound measurement of residual urine volumes.

Conventional cystometry and ambulatory monitoring were conducted as close together as possible. In 18 patients they were performed on consecutive days and for the remainder at a mean of 14 days apart.

Data are reported as means ± 1 standard deviation but were analysed by means of statistical tests suitable for non-parametric data. Unless otherwise stated, these were the Wilcoxon sign-ranked test or the Mann Whitney U test.

Results

Detrusor pressures

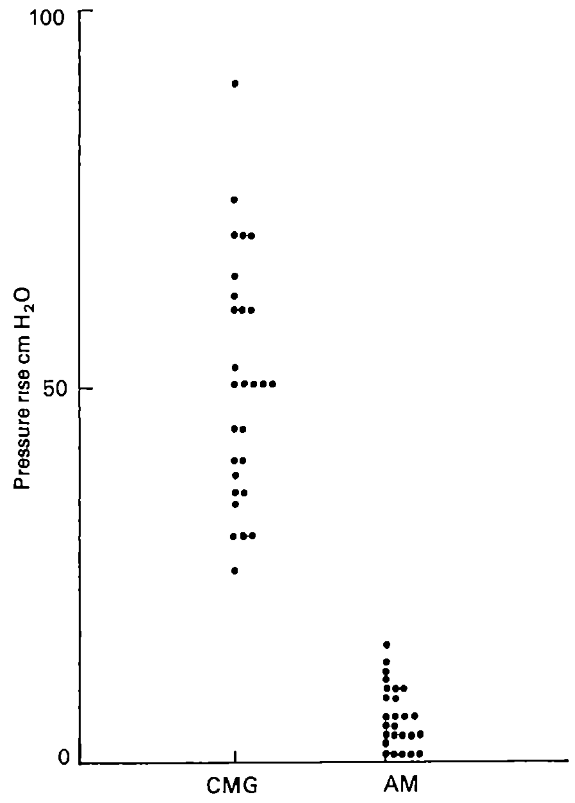
All patients exhibited low compliance and a high pressure rise on filling during conventional cystometry (pressure rise during filling 51.6 ± 23 cm H_2O). However, on ambulatory monitoring during natural bladder filling a significantly smaller pressure rise was observed (5.5 ± 5.1 cm H_2O; $Z = -3.29$, $P < 0.001$) (Fig. 1).

The filling volumes during AM and CMG were similar, at 276 ± 118 and 297 ± 145 ml respectively ($P = \text{ns}$). Thus a significant difference was found in measurements of bladder compliance (CMG compliance $= 4.9 \pm 2.7$ ml/cm H_2O; AM compliance $= 92 \pm 12$ ml/cm H_2O; $Z = -3.2$; $P < 0.001$).

In addition, 6 patients were studied during slow fill cystometry (20 ml/min) (Table 1). In broad terms, however, the values of pressure rise and compliance when the bladder was filled at 20 ml/min were intermediate between those obtained during AM and those obtained during filling at 100 ml/min.

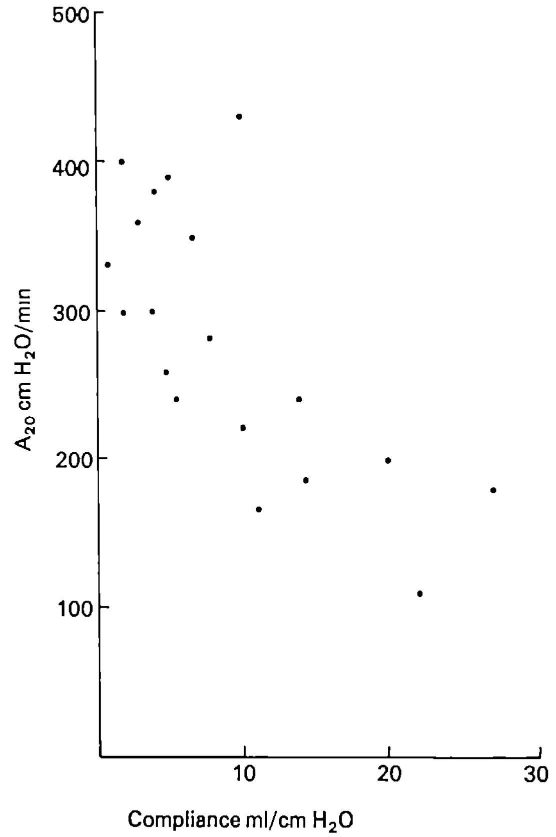
Phasic bladder activity

Table 3 shows that 8 patients exhibited phasic contractions during both investigations, a further 8 patients were stable on both tests, 1 patient had phasic contractions on CMG and was stable during AM, but 11 patients had phasic contractions during AM alone. Ambulatory monitoring was, therefore, more sensitive in detecting hyper-reflexia than



N=28 $P<0\ 001$

Fig. 1 Comparison of the rise in subtracted detrusor pressure during natural filling and medium fill cystometry



N=19 rs=0.76 $P<0\ 001$

Fig. 2 A20 hyper-reflexia (AM) compared with compliance (CMG)

conventional cystometry (McNemar's $X^2=6.75$, $P<0.01$).

The frequency of phasic contractions observed in those 19 patients who had phasic contractions on AM correlated inversely with the estimation of poor compliance during a conventional CMG (rs = 0.73; $P<0.001$). The A20 values, which combined both the frequency and amplitude of any phasic activity, when calculated for the 19 patients who had phasic contractions on AM correlated inversely with poor compliance (rs = 0.76, $P<0.001$) (Fig. 2).

When the analysis was repeated after exclusion of the 3 patients treated with a permanent indwelling catheter at the time of study, no differences were found in the results reported above.

Upper tract dilatation

The 6 patients with upper tract dilatation were

Table 1 Comparison of Detrusor Pressure Rise during Ambulatory Monitoring of Natural Bladder Filling, Slow Fill Cystometry and Medium Fill Cystometry in 6 Patients

	Natural bladder filling (AM)	*Slow fill cystometry (20 ml/min)*	*Medium fill cystometry (100 ml/min)*
Resting detrusor pressure (cm H_2O)	2.8±5	5±4	4±5
Detrusor pressure rise on filling (cm H_2O)	6±4	18±7	46±13
Compliance (cm H_2O)	114±32	8±2	6±3

Table 2 Comparison of Urodynamic Findings in Patients with and without Upper Tract Dilatation

	Dilated upper tracts	*Normal upper tracts*	*P*
No of patients	6	22	
Filling detrusor pressure rise CMG (cm H_2O)	58 ± 6	43 ± 8	<0.05
Residual urine (ml)	360 ± 115	223 ± 76	<0.001
Phasic detrusor activity LTM (contractions/h)	15 ± 6	8 ± 7	<0.001
A20	267 ± 101	118 ± 116	<0.001

Table 3 Comparison of Presence (+) or Absence (−) of Phasic Detrusor Contractions during Ambulatory Monitoring (AM) and Medium Fill Cystometry (CMG) in 28 Patients

		AM	
		+	−
CMG	+	8	1
	−	11	8

McNemar's $X^2 = 6.75$ ($P < 0.01$).

compared with the remaining 22 patients with normal upper tracts (Table 2). Significant differences were noted between the 2 groups with regard to residual urine volumes, compliance during CMG and frequency of phasic contractions during AM and A20.

Discussion

Our results support the findings of previous authors who found an association between upper tract dilatation and both high residual urine volume and poor compliance during medium fill cystometry (McGuire *et al.*, 1981, 1983; Rickwood *et al.*, 1982). However, during natural filling such high pressures were not observed. In addition, during natural filling a marked increase in phasic detrusor activity was found compared with artificial filling.

Previous work lends support to these findings. For example, the use of natural filling cystography was reported by Comarr in 1957. He observed in paraplegic patients who mainly had suprasacral lesions that bladder capacities were greater during natural filling. Also, Tonji *et al.* (1960) reported that pressures during natural filling in paraplegic patients were similar to those of a single normal patient, although pressures were observed to be greater in men with lesions of the sacral cord. In addition, Klevmark (1974, 1977) reported that normal compliance in the cat was recorded during natural filling or external filling at physiological rates of the intact, the sympathectomised or the parasympathectomised bladder. However, compliance fell if filling exceeded physiological rates by a factor of 2.4–7.

The rate of bladder filling is recognised to be important, particularly in the investigation of the neuropathic bladder (Thomas *et al.*, 1975) and our data support this suggestion. However, filling at 20 ml/min was also found to produce a significantly greater elevation of filling pressure compared with natural filling.

Our results are therefore in agreement with the data of Klevmark (1974, 1977) and support the idea that normal compliance is, in part, dependent upon intact neurological mechanisms. The role of filling pressures during natural filling in the development of upper tract dilatation remains an open question because we did not observe obviously raised pressures during natural filling and, moreover, could not separate those with upper tract dilatation from those with normal upper tracts on this parameter alone. On the other hand, high frequency phasic activity observed during natural filling was associated with low compliance during medium fill cystometry but was found less frequently during CMG.

The finding that bladders which had poor compliance on medium fill cystometry exhibited phasic activity during natural filling leads us to suggest that both abnormalities may be a reflection of the underlying abnormality of bladder muscle function produced by the neurological lesion. It may be that neither finding alone is responsible for upper tract dilatation, which may be caused by some, as yet, unidentified factor.

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Evaluation of the Home Pad Test for Quantifying Incontinence

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Summary—The home pad test to quantify urinary incontinence is described. Patients conduct the test in their homes and bring the pad, in a self-sealing plastic bag, for weighing at their next clinic visit. The validity of the procedure was assessed by measuring evaporation loss from the pads and comparing the home with the standard hospital test. Evaporation loss was shown to be acceptable if the test was carried out within 72 h of weighing. There were no significant differences between home and hospital tests and 95% of home results were within 32% below to 16% above hospital results. This was at least as consistent as the "gold standard" hospital test as 95% of the hospital results were within 28% below to 44% above repeated test results. The principal advantages in performing the pad test at home are simplicity, cost effectiveness and the relaxed environment, which reproduces more accurately the conditions leading to incontinence when compared with the relatively unfamiliar hospital setting.

The weighing or perineal pads (pad test) is now an accepted method for quantifying incontinence. This test, as initially proposed by Sutherst *et al.* (1981) and modified by the Standardisation Committee of the International Continence Society (1983), was intended for a hospital/clinic setting. However, there are advantages in conducting the test in the patient's home (Wilson *et al.*, 1980) as it reproduces more exactly the conditions which lead to incontinence. It is also significantly cheaper, since it does not involve medical/nursing supervision. For the past 2 years, patients in Dunedin have been pad tested in their own homes. They are given an instruction sheet and bring the pad in a self-sealing plastic bag to be weighed at their next clinic visit. An assessment of the validity of this home pad test has been carried out by measuring evaporation loss from pads in sealed bags and comparing the home with the standard hospital test.

Patients and Methods

Evaporated urine loss

Since the evaporation effects of urine and Ringer's lactate are similar (Wilson *et al.*, 1980), varying volumes (in duplicate) of Ringer's lactate (5–100 ml) were added to 11 pairs of pads, which were placed in self-sealing plastic bags ("Minigrip Handibags") measuring approximately 15 × 25 cm. The pads and bags were weighed daily for the next 7 days and the mean daily weights of each pair were compared to assess evaporation loss.

Comparison of home with hospital pad test

A group of 40 women was studied, 32 with urodynamically proven genuine stress incontinence, 3 with detrusor instability, 2 with detrusor instability and genuine stress incontinence and 3 post-operative colposuspension patients with no urodynamic abnormality. In an attempt to offset any learning effect during the tests the patients were consecutively allocated to 2 groups doing 2 pad tests in hospital followed by 2 at home or vice

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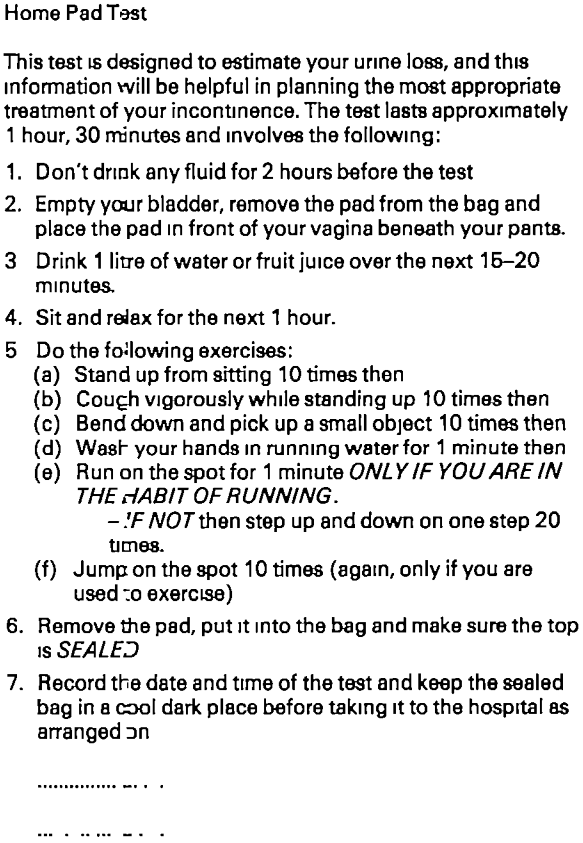
versa. All tests in each patient were done consecutively over 4 days. The pad test was a modification of that proposed by Sutherst (1981) and Klarskov and Hald (1983), the main differences being that patients were instructed not to drink for 2 h and to void before the procedure in order to standardise bladder volume for the test. For home tests, the procedure was explained to the patients (by P.D.W.) at their first clinic visit and they were given an instruction sheet (Fig.). Since the magnitude of the difference between pad tests was related to the amount of leakage, the data were initially transformed logarithmically. Correlation between home and hospital tests was assessed by the paired Student's *t* test and by calculating the 95% confidence intervals for the ratios of the results (Altman and Bland, 1983). The agreement between first and second hospital tests was measured in a similar manner.

Methods, definitions and units conform to the standards recommended by the International Continence Society.



Home Pad Test

This test is designed to estimate your urine loss, and this information will be helpful in planning the most appropriate treatment of your incontinence. The test lasts approximately 1 hour, 30 minutes and involves the following:

1. Don't drink any fluid for 2 hours before the test
2. Empty your bladder, remove the pad from the bag and place the pad in front of your vagina beneath your pants.
3. Drink 1 litre of water or fruit juice over the next 15–20 minutes.
4. Sit and relax for the next 1 hour.
5. Do the following exercises:
   - (a) Stand up from sitting 10 times then
   - (b) Cough vigorously while standing up 10 times then
   - (c) Bend down and pick up a small object 10 times then
   - (d) Wash your hands in running water for 1 minute then
   - (e) Run on the spot for 1 minute *ONLY IF YOU ARE IN THE HABIT OF RUNNING*.
     - *IF NOT* then step up and down on one step 20 times.
   - (f) Jump on the spot 10 times (again, only if you are used to exercise)
6. Remove the pad, put it into the bag and make sure the top is *SEALED*
7. Record the date and time of the test and keep the sealed bag in a cool dark place before taking it to the hospital as arranged on

....

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Fig. Instruction sheet

Results

Evaporated urine loss

The results of the evaporation loss from the pads in the self-sealing packets are summarised in the Table. On the day following the addition of Ringer's lactate to pads, the loss varied from 0.04 g (0.8%) after 5 ml were added to 0.13 g (0.13%) after 100 ml were added. By the third day this loss was 0.21 g (4.2%) and 0.29 g (0.29%) respectively.

Comparison of home with hospital pad test

There was no significant difference between the means of the home and hospital tests (home 26.0 g, hospital 21.2 g, $P = 0.375$) and the 95% confidence interval for the ratio of the home to the hospital result was (0.68, 1.16). Similarly, there was no significant difference between the first and second hospital tests (first test 23.7 g, second test 18.5 g,

Table Evaporation Loss From Pads in Self-sealing Bags

	Day 0	*Day 1*			*Day 3*			*Day 7*		
Volume added (ml)	*Mean pad wt (gm)*	*Mean pad wt (gm)*	*Loss (gm)*	*Loss (%)*	*Mean pad wt (gm)*	*Loss (gm)*	*Loss (%)*	*Mean pad wt (gm)*	*Loss (gm)*	*Loss (%)*
5	22.27	22.23	0.04	0.8	22.07	0.21	4.2	21.82	0.45	9.0
10	27.31	27.25	0.06	0.6	27.10	0.22	2.2	26.88	0.44	4.4
20	36.69	36.62	0.08	0.4	36.44	0.25	1.3	36.21	0.48	2.4
30	46.93	46.88	0.05	0.17	46.82	0.12	0.4	46.45	0.49	1.6
40	56.61	56.52	0.09	0.23	56.34	0.27	0.68	56.08	0.53	1.3
50	66.01	65.92	0.09	0.18	65.77	0.24	0.48	65.54	0.47	0.94
60	76.50	76.44	0.06	0.1	76.29	0.21	0.35	76.11	0.39	0.65
70	86.43	86.36	0.07	0.1	86.23	0.21	0.3	86.00	0.43	0.61
80	95.61	95.51	0.10	0.13	95.41	0.21	0.26	94.80	0.81	1.01
90	106.03	105.94	0.10	0.11	105.81	0.23	0.26	105.63	0.41	0.46
100	116.36	116.24	0.13	0.13	116.07	0.29	0.29	115.84	0.53	0.53

$P=0.932$) and the 95% confidence interval for the ratio of the first and second test was (0.72, 1.44).

Discussion

The results confirm the validity of the home pad test for quantifying incontinence. Evaporation loss from pads in sealed bags was shown to be acceptable if the test was carried out within 72 h of weighing, since on the third day this loss was 4.2% with 5 ml of fluid and 0.3% with 100 ml added to the pad. Our practice is to ask patients to perform the test on the day before their clinic visit, since evaporation loss at the various volumes was less than 1%. Comparison of home with hospital tests indicates that 95% of home results would be within 32% below to 16% above the hospital results and this is at least as consistent as the "gold standard" hospital results (95% of hospital test results would be within 28% below to 44% above repeated test results).

The principal advantages of the home pad test are simplicity and cost saving, since it does not involve medical/nursing supervision. In addition, the home environment and consequent patient relaxation may reproduce more exactly the conditions leading to incontinence when compared with the relatively unfamiliar hospital setting.

The pad test carried out in hospital or the patient's home has been shown in this study to have only moderate reproducibility but it remains adequate to classify incontinence into the 4 categories proposed by the Standardisation Committee of the International Continence Society (1983) (under 2 g, essentially dry; 2–10 g, slight to moderate loss; 10–50 g, severe loss; over 50 g, very severe loss). Its main purpose is an objective indicator of the severity of incontinence and a guide to management, with particular relevance to genuine stress incontinence (Haylen and Sutherst, 1987). The pad test helps to identify women who will benefit most from physiotherapy since mild/moderate incontinence is improved more consistently than severe leakage (Wilson *et al.*, 1987). If the test is used to assess the effects of treatment, caution should be exercised in interpreting results as these can only be judged to be significantly different from pretreatment values if they lie outside the confidence limits outlined above.

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Painful Bladder Syndrome—a Clinical and Immunopathological Study

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Summary—Painful bladder syndrome is a clinical diagnosis in patients with symptoms of varying severity which always include frequency and suprapubic pain and occasionally include dysuria, nocturia and urgency persisting for more than 3 months with no loss of bladder capacity and no overt infection.

Immunofluorescence studies of biopsy specimens in 38 female patients were assessed and correlated with the duration and severity of symptoms, and also with routine histology (including mast cell infiltration and integrity of the glycosaminoglycans layer), in order to assess the role of immunological mechanisms in this distressing condition.

The results indicated that submucosal angiogenesis and persistence of antigen-antibody complex in vessel walls could be responsible for this syndrome.

Classic interstitial cystitis (IC) has long been recognised as a clinical syndrome presenting in many guises, with characteristic ulceration of the bladder resulting in fibrosis and loss of vesical capacity (Hunner, 1915; Smith and Dehner, 1972). An immunological mechanism has been proposed in the aetiology of this disease (Gordon *et al.*, 1973; Mattila, 1982). We present a group of patients who, although manifesting clinical symptoms reminiscent of IC, did not have typical ulceration at cystoscopy. Early IC has been previously recognised as a separate entity (Lapides, 1975; Messing and Stamey, 1978; Fall *et al.*, 1985). We would define these patients as having painful bladder syndrome (PBS)—a clinical diagnosis in patients who invariably complain of frequency and suprapubic pain; they may also suffer from dysuria, nocturia and urgency persisting for more than 3 months with no loss of bladder capacity and the absence of overt infection. The object of this study was to define further the histological and immunohistochemical features of PBS and to correlate these with the clinical findings. Thus the significance of the underlying pathology could be evaluated from both diagnostic and therapeutic viewpoints.

Patients and Methods

A group of 38 female patients with symptoms of PBS was evaluated by the following methods:

1. Symptoms were assessed for severity, type and duration.
2. A mid-stream urine sample was obtained for microscopy and culture.
3. All patients underwent cystoscopy with evaluation of vesical capacity under anaesthesia; the macroscopic appearances of the bladder were noted.
4. Biopsies of 2 adjacent areas (including any abnormality) were obtained prior to distension; the first specimen was placed in formalin for routine processing; 4 μ paraffin wax sections were stained with haematoxylin and eosin, toluidine blue for mast cells and acid alcian blue to assess the integrity of the glycosaminoglycans layer (GAG). The second specimen was placed in transport medium, snap frozen and frozen sections stained by standard methods for im-

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munofluorescence for IgA, IgG, IgM, C3 and fibrinogen, using a direct technique; 15 formalin fixed biopsies were also stained by MB2 immunoperoxidase method (Hall *et al.*, 1987) to assess B cell infiltrate.

A control group of 10 patients, undergoing check cystoscopy for unrelated conditions with no symptoms of PBS, was similarly biopsied for histological assessment as above.

Results

The patients ranged in age from 18 to 36 years (median 42). The distribution by age was bimodal, with peaks in the 18 to 30 year group and 60 year+ group. They presented with a wide variety of symptoms (dysuria, nocturia, urgency) but all had frequency and suprapubic pain. All MSUs were sterile at the time of presentation but 6 patients had previous documented infection (all *Escherichia coli*) and 2 had once had haematuria. A history of documented infection was difficult to obtain from the patients' general practitioners. Many had been treated empirically, most frequently with nitrofurantoin, erythromycin or tetracycline. Vesical capacity ranged from 350 to 700 ml for all patients. At cystoscopy none showed typical signs of IC (ulceration and scarring); 33 had areas of reddening with neovascularity and 5 had normal cystoscopic appearances, although all showed petechial haemorrhages following distension. On routine histological assessment, 81% showed intact transitional epithelium with a chronic inflammatory infiltrate, oedema and telangiectasia in the submucosa. Telangiectasia was absent in 19% but all patients showed an increase in chronic inflammatory cells in the submucosa (Fig. 1).

The results of immunofluorescence are shown in Figure 2 and are grouped according to the site of immunofluorescence: either surface and/or vascular deposition. All patients (6) with vascular immunofluorescence showed IgM deposits: 1 patient also showed C_3 and 3 in addition had fibrinogen. In surface (S) and vascular (V) positivity, IgM alone was present in 4 of 5 patients. In surface IgA positivity this was sited on the umbrella layer and occasionally throughout the epithelium. No IgG positivity was present in any site studied. Fifteen biopsies were stained with MB2 and B cell precursors were scored + or + + according to site (Table).

The severity of symptoms (3 or more symptoms, frequency > 8/day) showed a good correlation with

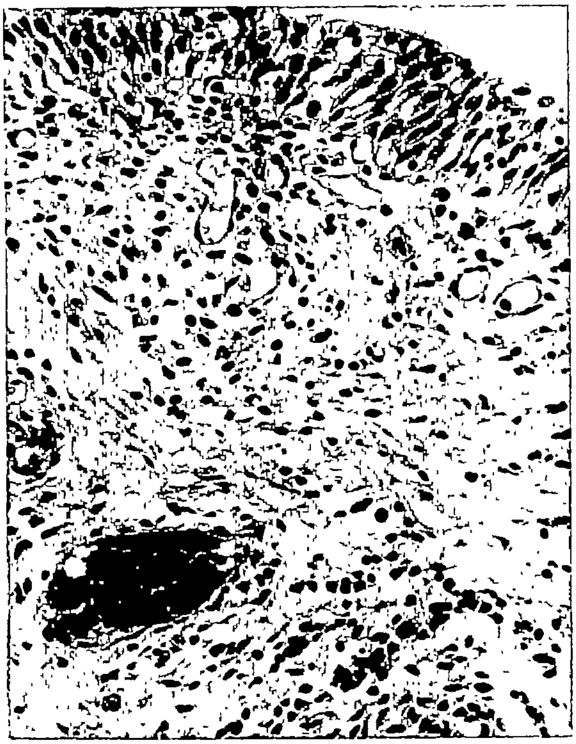

Fig. 1 Bladder mucosa showing submucosal telangiectasia, oedema and a marked chronic infiltrate (H and E × 250)

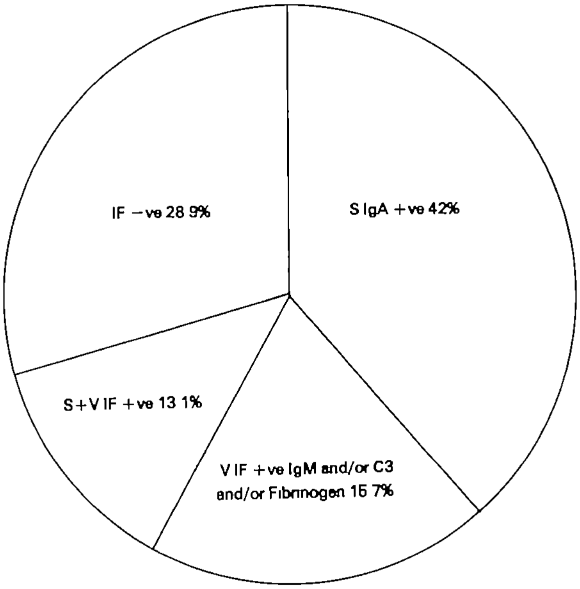

Fig. 2 Results of immunofluorescence studies IF = immunofluorescence. S = surface. V = vascular.

Table Results of MB2 Immunoperoxidase Staining

	IF V IgM C_3 Fibrinogen	*V IgM*	*S IgA*	*−ve IF*	*Total*
SM++ and PV++	3				3
SM++			3	1	4
SM+		4	2	2	8
					15

IF = immunofluorescence.
SM = submucosa.
PV = perivascular
S = surface
V = vascular

positive immunofluorescence ($P<0.0001$). The presence of chronic inflammation, telangiectasia and oedema and the presence of more than 5 mast cells/HPF in the submucosa also showed good correlation with positive immunofluorescence ($P<0.01$ and $P<0.0001$ respectively). However, an intact or absent GAG layer did not correlate with positive immunofluorescence ($P>0.05$), nor did the duration of symptoms in yearly intervals ($P>0.05$).

Discussion

Painful bladder syndrome is a poorly understood condition defined by a combination of clinical and pathological features. Little is known of its pathogenesis or natural history. The object of this study was to define the histological and immunohistochemical findings in a clinically well defined group of patients and to see if these could be correlated with the severity and duration of symptoms. In the absence of a demonstrable infective organism, the role of immunological mechanisms in the initiation and promotion of bladder injury was of particular interest.

It has been postulated that the sequence of events in PBS is initiated by disruption of the integrity of the glycosaminoglycans (GAG) layer of the bladder epithelium. GAG is a protective layer preventing adherence of bacteria to the bladder mucosa (Parsons *et al.*, 1975, 1977, 1980; Shrom *et al.*, 1977, Parsons and Mullholland, 1978). This allows urine, and possibly the initiating agent (be this infective or otherwise), to gain access to the underlying tissue (Parsons *et al.*, 1983). This antigenic stimulation produces an immunological response—chiefly IgA (Uehling and Steihm, 1971; Parsons *et al.*, 1983). The latter persists despite apparent regeneration of the GAG layer, which may occur within 48 h (Parsons *et al.*, 1977). The present study supports this view by showing no correlation between the presence of an intact GAG layer and positive immunofluorescence. However, good correlation was observed between immunopositivity and severity of symptoms. It was observed that IgM deposition in vessel walls was associated with severe symptoms but the number of patients was too small to be analysed statistically. There appear to be 2 possible mechanisms involved: (1) positive IMF in vessel walls, and therefore humoral immune mechanisms, may be responsible for producing the histological features of chronic inflammation, telangiectasia and symptomatology; (2) the increased numbers of mast cells which correlated with these findings are presumably induced in this process and cause pain by production of kinins and angiogenesis by release of endogenous heparin (Williams and Gibbons, 1972). The histology at this stage reflects the pathological process with an intact GAG layer, surface IgA deposition and/or vessel immunofluorescence, a chronic inflammatory response with oedema, telangiectasia and increased numbers of mast cells. B cell staining supports the view that local humoral mechanisms are in force. Larsen *et al.* (1982) also found increased numbers of mast cells in IC. In the presence of steroid, heparin has anti-angiogenic effects, thus justifying a treatment rationale of low molecular weight heparin with steroid in DMSO acting as a carrier to the site of damage (Ingber *et al.*, 1985). This regimen brought significant relief in 5 patients in whom vascular IgM deposition had been noted prior to treatment. A trial of intravesical DMSO and steroid alone did not improve symptoms in these 5 patients. This suggests that new vessel formation (with persistence of antigen-antibody complex in vessel walls) might be responsible for the continuing misery of PBS and that anti-angiogenic treatment would be beneficial. Studies are in progress to assess the efficacy of different types of treatment.

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Urethral Stricture Following Aortic Graft Surgery

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Summary—The incidence of urethral stricture following aortic graft surgery was investigated retrospectively in a group of 127 men. They had been catheterised prior to their operation with latex catheters. One man had been treated for a stricture 9 months after his operation. Information about post-operative urinary symptoms was obtained from a further 94 surviving patients by postal questionnaires sent at least 12 months following surgery. Eight patients underwent urological review including, where indicated, urethrography under antibiotic cover; 3 patients were identified with urethral strictures, an incidence of 3.2%. This is similar to that occurring after cardiac surgery, and urethral strictures should be considered a hazard whenever catheters are used in surgical procedures.

Urethral strictures are a recognised complication in patients undergoing coronary artery surgery (Ruutu *et al.*, 1982; Sutherland *et al.*, 1983; Ferrie *et al.*, 1984). Similar strictures have been found in patients who have been catheterised for other procedures. Aortic grafting is a frequently performed standard surgical procedure during which patients are routinely catheterised. A group of men undergoing this operation over a 1-year period was studied retrospectively to assess the incidence of such strictures.

Patients and Methods

A total of 127 men underwent elective aortic graft surgery in the Peripheral Vascular Surgery Unit between August 1984 and July 1985. All were catheterised with 14F latex catheters using sterile KY jelly as lubricant. Standard practice was for the catheters to be removed between 12 and 24 h after operation unless longer monitoring of urinary output was indicated.

A questionnaire on the post-operative development of urinary symptoms was prepared. This was sent to the 120 patients thought to be alive, via their general practitioner, just over 12 months after the last patient had undergone his operation. Any patient whose reply suggested that he had significant symptoms was invited to see one of us (D.K.) and, if indicated following a more detailed history, a urethrogram was performed using a single intravenous injection of netilmicin as antibiotic prophylaxis

Results

One man from the original 127, who died before our survey, had developed a stricture 9 months after his operation, and it was his referral to one of us that prompted the survey. Information was obtained about a further 104 patients; 10 more were found to have died and questionnaires were returned by 94 survivors. Abnormal urinary symptoms were reported by 12 patients and they were asked to attend for review; 8 did so. Urethrograms were performed in 5 patients and 2 showed strictures subsequently confirmed on urethroscopy. Of the remaining 3 patients, 2 had a stricture excluded by cystourethroscopy and 1 was considered too frail and confused to undergo further investigation. In addition, a patient with urinary symptoms was known to have undergone transurethral prostatectomy at another hospital with no evidence of a urethral stricture having been found. Including the man previously mentioned who died before the survey took place, 3 strictures were known to have occurred among 95 patients, an incidence of 3.2%, diagnosed from 9 to 21 months after aortic surgery; 2 patients had short posterior urethral strictures and 1 a dense funnelled submeatal stricture with

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beading of the remainder of the urethra, a type of stricture which would now be considered typical of the strictures seen after cardiac surgery (Ruutu *et al.*, 1982).

Discussion

Since information is available on only 95 of the original patients, and since only 8 of 12 patients known to have abnormal urinary symptoms were available for investigation, the incidence of 3.2% must be considered approximate. This is possibly an under-estimate, since it is known that 1 of the patients who died before the survey was undertaken was suffering from symptoms suggestive of a stricture, and we have not excluded strictures in 3 of the symptomatic patients who did not attend for review. Including the patient whose stricture was diagnosed before the survey took place, these strictures were discovered between 9 and 21 months after operation. The incidence compares with that of 5.2% in the previous reported group of patients following cardiac surgery (Ferrie *et al.*, 1986). At the time of surgery, latex catheters were used in both of these groups of patients and it would seem that the incidence of stricture was similar in both groups. One of us has treated a number of patients with severe urethral strictures where the only aetiological factor appeared to be catheterisation for indications as varied as major head injury, hip replacement or colo-rectal surgery. We had intended to study men catheterised for large bowel resection in addition to those undergoing aortic surgery, but most of those undergoing colonic resection did so for cancer and insufficient numbers of patients survived long enough for a valid survey to be possible. However, strictures of the type described here and after cardiac surgery have been seen in such patients. In male patients presenting with urinary symptoms, and where patients have been catheterised, a diagnosis of urethral stricture must be seriously considered.

Urethral ischaemia has been suggested as a possible mechanism for stricture formation after cardiac surgery (Abdel-Hakim *et al.*, 1983; Elhilali *et al.*, 1986). In men undergoing aortic graft operations it is possible that there could be urethral ischaemia during cross-clamping of the aorta. However, it is of interest that during the survey an additional patient came to light who developed a urethral stricture following catheterisation during a femoro-popliteal by-pass graft where the aorta was not cross-clamped and in whom urethral ischaemia during surgery was therefore unlikely.

The routine use of silicone catheters has been shown to reduce the incidence of post-cardiac surgery strictures (Sutherland *et al.*, 1983; Ruutu *et al.*, 1984; Nacey *et al.*, 1985; Ferrie *et al.*, 1986), suggesting that catheter material is more important than ischaemia in stricture formation. An anti-oxidant used by the manufacturers of latex catheters prior to 1983 has been considered a possible cause of strictures. Such catheters may have been used in the cardiac surgery patients we have previously studied (Ferrie *et al.*, 1984). The patients undergoing aortic grafts in this survey were catheterised between August 1984 and July 1985. Although there is no record of the catheters used, it is possible that pre-1983 catheters containing the anti-oxidant in question were still available at this time.

In the past it has been suggested that particularly high incidences of urethral strictures have been associated with faulty batches of catheters. Blacklock (1986) pointed out that each urethral catheter is coded with a number which allows it to be traced back to its original batch; perhaps this information should be recorded in the case notes when a man is catheterised for a routine operation to enable such "rogue" batches to be indentified, catheter manufacturers are now aware of this problem, however, and we hope that the new methods of testing will avoid this problem in future.

While post-catheterisation strictures might be considered uncommon (Blacklock, 1986), we feel that an incidence of 3 to 5% in men undergoing short periods of catheterisation for non-urological procedures must be considered unacceptable. We recommend that the indications for routine pre-operative catheterisation, or indeed the use of a catheter in any circumstances, be carefully re-evaluated. We know of one vascular surgeon who has abandoned routine catheterisation in patients undergoing elective aortic grafts specifically to avoid the risk of urethral strictures. Where a catheter is considered essential, it would seem sensible to use a silicone rather than a latex catheter (Ferrie *et al.*, 1986) and this is now the practice in the Peripheral Vascular Unit at Glasgow Royal Infirmary. A new type of latex catheter which is said not to contain the toxic materials thought to be the cause of urethral strictures has now been developed; *in vitro* toxicity testing with these catheters is encouraging, but their clinical safety has yet to be evaluated.

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Initial Management of Acute Urethral Injuries

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Summary—A study was made of 30 cases of acute urethral trauma treated over a 7-year period. There were 10 anterior and 20 posterior urethral injuries, the majority of these being partial ruptures. Posterior urethral injuries were caused by road traffic accidents in 75% of cases while 80% of the anterior urethral injuries were of the "straddle" type. There was only 1 case of iatrogenic injury to the anterior urethra.

During follow-up, all patients required periodic dilatations for stricture except for the single case of iatrogenic injury. An average of 5 dilatations controlled all of the strictures except for 2 that required urethroplasties.

The management of acute trauma to the urethra has always been a challenge. Despite the best judgement and surgical skill, strictures almost inevitably develop. Thus controversy continues regarding preliminary diversion and a planned repair (Morehouse *et al.*, 1972; Mitchell, 1975; Coffield and Weems, 1977), diagnostic catheterisation or railroading, or both (Jackson and Williams, 1974; Blandy, 1975; Malek *et al.*, 1977).

Patients and Methods

Thirty cases of traumatic injury to the urethra were collected for review over a 7-year period (1977–1983). Patients with associated rupture of the bladder were excluded. The age of the patients ranged from 20 to 75 years (mean 36) (Fig. 1). The majority were Chinese and all were male.

Mode of injury (Table 1)

The commonest cause was road traffic accident caused by motorcycles (8) and larger vehicles (7). A "straddle" type of injury occurred in 8 patients. However, there was 1 case of partial rupture of the penile urethra during dilatation for a short anterior urethral stricture.

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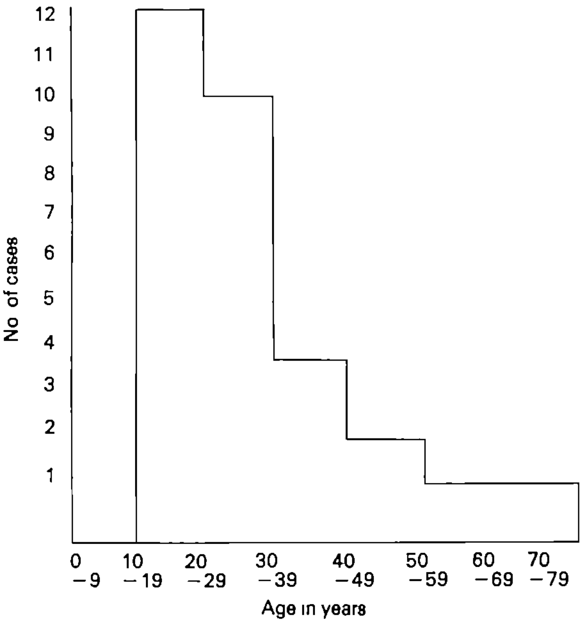

Fig. 1 Incidence of urethral injuries charted against age in decades.

Presentation (Table 2)

Eleven patients complained of blood at the urethral meatus, 17 could not pass urine and in 13 cases there was an associated fracture of the pelvis (Table

Table 1 Mode of Injury

	No
Road accidents	
Motorcycle	8
Car, lorry	7
Falling astride	8
Crush	0
Falling bricks/others	3
Metal bar	3
Games	0
Iatrogenic	1
Total	30

Table 2 Presentation

	No
Anterior urethral injuries	
Palpable bladder	1
Unable to void	6
Blood at external meatus	7
Perineal haematoma	10
Posterior urethral injuries	
Palpable bladder	3
High riding prostate	4
Blood at external meatus	4
Perineal haematoma	8
Unable to void	11
Fractured pelvis	13

Table 3 Extent of Pelvic Fracture

	No.
Fractured pubic ramus	2
Fractured pubic rami	5
Diastasis of symphysis pubis	2
Diastasis of symphysis pubis and fractured pubic rami	3
Fractured ilium, Lt. acetabulum and Lt pubic ramus	1
Total	13

3). In 18 patients a perineal haematoma was obvious. Digital rectal examination revealed a high riding prostate gland in the 4 cases of complete rupture of the posterior urethra. A palpable bladder was found in only 3.

Urographic studies

Some form of contrast study was performed urgently in 7 patients; this consisted of intravenous urography in 3 and ascending urethrography in 4 who were thought to have complete transection of the posterior urethra. In 6 patients who had suprapubic cystostomy only, a urethrogram was done 3 weeks after the injury to assess the post-traumatic stricture and in a further 2 a micturating cystourethrogram was done 2 months after formal urethroplasty. There was no definitive policy for ordering contrast studies; it was left to the discretion of the surgeon.

Site of injury

There were 10 anterior and 20 posterior urethral injuries, only 4 of which were complete ruptures. Most of the anterior urethral injuries were located at the bulbar area while the membranous urethra was the site of those in the posterior urethra.

Treatment (Fig. 2)

Early management. Successful voiding occurred in 4 patients with anterior (bulbar) injuries. In 7 cases with obvious urethral injury clinically, 3 underwent immediate suprapubic cystostomy only, while 4 had railroading with suprapubic catheterisation after an urgent urethrogram. In the remainder, a trial of catheter was successful in 9 of 19: of the failures, 3 underwent suprapubic cystostomy only, 6 had railroading and a suprapubic catheter plus a laparotomy if intra-abdominal injury was suspected, and 1 patient with partial rupture of the penile urethra during dilatation had an immediate anastomotic urethroplasty after excision of the short stricture together with temporary suprapubic cystotomy.

Late management. After an interval of 3 weeks, each patient (excepting those where urethrography was done) was assessed by examination under anaesthesia and urethral calibration.

Results

Urethrography and urethral calibration revealed a stricture in all cases, except for the single patient with a primary anastomotic urethroplasty, and periodic dilatations were required; the average number was 5, with a range of 5 to 36 over a 3-year period. One case of posterior urethral stricture and 1 of penile stricture responded poorly to dilatation; the former underwent a free scrotal skin tube urethroplasty and the latter a direct excision and anastomotic urethroplasty. Two patients had incontinence, 2 impotence and 1 complained of failure of ejaculation.

Discussion

In this series, as in others, rupture of the posterior urethra occurred most frequently when there was an associated fractured pelvis caused by a road

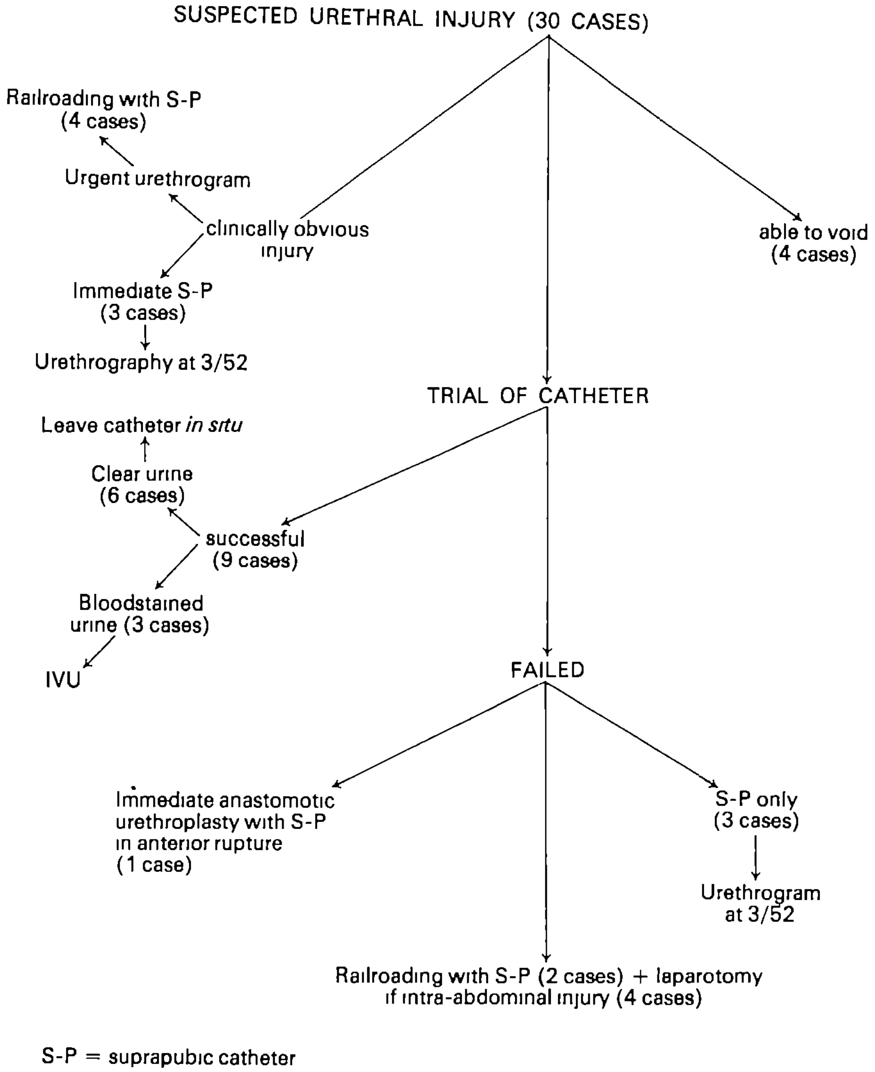
SUSPECTED URETHRAL INJURY (30 CASES)
Railroading with S-P (4 cases)
Urgent urethrogram
clinically obvious injury
Immediate S-P (3 cases)
Urethrography at 3/52
able to void (4 cases)
TRIAL OF CATHETER
Leave catheter *in situ*
Clear urine (6 cases)
successful (9 cases)
Bloodstained urine (3 cases)
IVU
FAILED
Immediate anastomotic urethroplasty with S-P in anterior rupture (1 case)
S-P only (3 cases)
Urethrogram at 3/52
Railroading with S-P (2 cases) + laparotomy if intra-abdominal injury (4 cases)
S-P = suprapubic catheter

Fig. 2 Initial treatment of acute urethral injuries

traffic accident (Mitchell, 1967; Glass *et al.*, 1978; Turner Warwick, 1985). There are 3 schools of thought on the early management of urethral injuries (Table 4). We used the diagnostic catheter in the majority of our patients; it indicated the diagnosis and was therapeutic in nearly half of the cases where it was used. We have not encountered the often quoted dangers of the diagnostic catheter, *i.e.* risk of infection (Culp, 1942; Villet, 1961), risk of further damage to the partially ruptured urethra (Mitchell, 1963) and risk of a false diagnosis (Culp, 1947; Constantin and Felton, 1952).

Many authors advocate the use of retrograde urethrography (Fowler *et al.*, 1986) but nearly all admit that it has its limitations (McCrea, 1940; Culp, 1942; Weens *et al.*, 1946; Holland *et al.*, 1966; Rieser, 1967; Veiga-Pires and Elebute, 1967).

We have treated our ruptures of the posterior

Table 4 Approach to Early Treatment of Urethral Injuries

Conservative (Mitchell, 1973)	Suprapubic catheter followed by urethrography and urethroscopy at 3 weeks
Semi-conservative (Coffield and Weems, 1977)	Retrograde urethrography and cystography followed by suprapubic catheter
Aggressive (Blandy, 1975)	Trial of catheter. If unsuccessful, proceed to urethrography and exploration

urethra mainly by railroading (Foreman, 1959) and applying traction to a splinting balloon catheter. The period of traction is limited to 3 to 4 days. We have had no occasion to use Kisner's perineal stitch or Carswell's method of fixing the prostate with stitches over the symphysis pubis (Carswell, 1957). We leave a suprapubic catheter in the bladder and a corrugated drain in the perivesical space. A course of antibiotics (ampicillin) is used routinely in the post-operative period. We recommend the use of a catheter no larger than 16 F in anterior urethral injuries. The modern siliconised variety is preferred and may be left for 7 to 10 days in the presence of a minimal urethral tear and no extravasation. Where extravasation of blood or urine, or both, can be demonstrated, incision and drainage as emphasised by Devine *et al.* (1977) may be necessary. Although our experience of primary excision and re-anastomosis of short anterior strictures is limited, we believe that it can give good results (Allen, 1977; Turner Warwick, 1985).

Stricture is inevitable in complete transection of the urethra (Mitchell, 1968) and almost inevitable in partial disruptions. The average number of dilatations used to treat these strictures was 5. Only 2 patients required such frequent bouginage that planned urethroplasties were finally done.

Only 2 patients complained of incontinence and they improved with conservative measures. In assessing sexual dysfunction, we discovered that most patients were fully potent within a year from the time of injury. The 2 patients who were impotent were men in their sixties or seventies who claimed that they were potent prior to the accident. Dalton (1983) stated that impotence occurred in 25 to 75% of patients with complete rupture of the posterior urethra and incontinence in 5 to 25%.

Traumatic injuries of the urethra are serious injuries. Controversies centre on the acute management of these injuries. Straddle injuries are satisfactorily managed in most instances by retrograde catheterisation with a small calibre catheter; injuries of the posterior urethra are best treated by classical "railroading". However, in the absence of expertise, facilities, or both, simple suprapubic diversion has a definite role in primary management.

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The Failed MAGPI: Management and Prevention

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Summary—Of 142 patients with hypospadias seen at this institute over the past 2 years, 8 developed meatal regression following repair of their anterior hypospadias with the meatal advancement and glanuloplasty technique (MAGPI); 5 had meatal regression which was attributed to a technical failure and 3 had severe regression of the meatus with significant subcoronal positioning, suggesting poor patient selection. None of these patients had chordee on intra-operative artificial erection. Five were treated successfully with a repeat MAGPI procedure and the remaining 3 required a Mathieu procedure. Although best indicated for mild degrees of anterior hypospadias, the success of the MAGPI procedure still requires meticulous technique and proper patient selection.

Hypospadias is a common congenital defect occurring in 8.2/1000 live male births (Sweet *et al.*, 1974). Anterior hypospadias accounts for 70 to 87% of all hypospadias (Sweet *et al.*, 1974; Duckett, 1981) and can be further subdivided according to the exact location of the opening into glandular, coronal and subcoronal hypospadias. In the past, surgical repairs were concentrated on patients with more proximal hypospadias. Distal hypospadias repair was somewhat neglected because its surgical correction was complicated and many urologists felt that subjecting such a patient to surgery was both unnecessary and unjustified.

It was not until 1981, when the MAGPI procedure was reported, that patients with anterior types of hypospadias began to receive proper surgical attention (Duckett, 1981). Since then the MAGPI has proved to be a simple, safe and reliable procedure (Livne *et al.*, 1984; Man *et al.*, 1984) and an increasing number of patients are undergoing surgical repair with this technique. However, one of the MAGPI's most common complications is the development of meatal regression. We report 8 such patients and outline the possible reasons for its occurrence and our management of this problem.

Patients and Methods

Of 142 patients with hypospadias seen over the past 2 years, 8 developed meatal regression following repair of their anterior hypospadias with the MAGPI technique (Duckett, 1981). All had undergone surgery at other hospitals by consultant urologists. Their ages ranged from 2 to 15 years (mean 6.8). On physical examination, the meatal regression was evident in all patients; 5 (group A) had a minor degree of regression and 3 (group B) had more marked regression of the meatus beyond the coronal region (Table, Fig.).

Surgical repair was performed on all patients and included repeating the MAGPI procedure in 5 (group A), while the other 3 underwent a Mathieu (1932) procedure. The 6 prepubertal patients received testosterone enanthate 2 mg/kg intramuscularly 5 and 2 weeks prior to surgery. None had chordee on intra-operative artificial erection. An 8 F Foley catheter was left overnight in those patients who underwent a repeat MAGPI procedure. In those treated by a Mathieu repair, an indwelling No. 8 Silastic stent was left for 8 days.

Results

All patients were reviewed 3 months after surgery and all had a satisfactory cosmetic result as judged

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Table Type of Hypospadias and Age Distribution of 8 Patients with Meatal Regression Following MAGPI

	*Group A**					*Group B†*		
	I	*II*	*III*	*IV*	*V*	*VI*	*VII*	*VIII*
Original meatus	Coronal	Glandular	Coronal	Sub-coronal	Sub-coronal	Distal shaft	Distal shaft	Distal shaft
After MAGPI	Coronal	Coronal	Coronal	Coronal	Coronal	Distal shaft	Distal shaft	Distal shaft
Age (years) at original MAGPI	3	11	2	11 5	1.5	1.5	1 5	7
Age (years) at second repair	5	15	3	13.5	2	2	3	11

*Repeat MAGPI †Mathieu repair

Fig. Regression of urethral meatus to distal shaft area after MAGPI procedure 1½ years previously

by the parents and surgeon. The urethral meatus was at the tip of the penis and all were voiding a singular urinary stream with no evidence of fistula.

Discussion

The MAGPI procedure has proved to be the best treatment for the management of anterior hypospadias (Duckett, 1981). The simplicity and lower complication rate of this treatment make it preferable to the previously described procedures of Mathieu (1932), Devine and Horton (1977) and King (1970). Complications following the MAGPI procedure, although rare, do occur. Meatal regression, fistula formation and meatal stenosis have all been reported. Ozen and Whitaker (1987) reported a complication rate of 9%. Such complications defeat the original intent of the repair and create new problems necessitating further surgical procedures.

Meatal regression following the MAGPI procedure has been reported to occur in 3 to 6% of patients (Livne *et al.*, 1984; Man *et al.*, 1984). The cause of the meatal regression is speculative. One possible contributing factor is the presence of chordee. However, in a series of 66 patients, Livne *et al.* (1984) reported only 2 with meatal regression, none of whom had chordee. By contrast, in the series of 67 patients reported by Ozen and Whitaker (1987), 3 of the 4 patients with meatal regression had moderate to severe chordee. It is of interest that 25 of the 29 patients with chordee, in that same series, enjoyed good results following the MAGPI procedure. In our series of failed repairs, no patient had chordee and we are not convinced that the presence of chordee alone is the main reason for the development of meatal regression.

Both proper patient selection and good surgical technique play an important role in the success of the MAGPI procedure. When considering the former, it is felt that patients in whom the meatus lies proximal to the subcoronal region are not suitable candidates. In our patients with the most severe degrees of regression, the original meatus was on the distal penile shaft. Thus 3 of our patients (group B) fell into this category of poor patient selection. Good surgical technique, on the other hand, requires meticulous attention to the provision of a tension-free glandular and skin closure. Tension on the urethral meatus by the glans penis may contribute to the development of meatal regression. In our 5 patients with mild degrees of regression, a repeat MAGPI procedure was easily accomplished, thus suggesting tension on the original glandular closure with resultant glandular separation and meatal retraction.

The treatment for meatal regression is a repeat MAGPI as long as the regression is of mild degree, the remaining ventral skin is adequate and the meatus lies in a suitable position with adequate mobility for further advancement. These conditions were met in 5 of our 8 patients (group A). In patients with more (or less) severe regression and inadequate meatal mobility, other techniques must be used. In our 3 patients with severe meatal regression following a MAGPI procedure, a Mathieu (1932) procedure was easily performed.

A meatal-based flap might seem risky, since the skin proximal to the meatus may have been previously transected. However, our patients had sufficient amounts of ventral skin and the flaps were kept very thick to ensure viability. If however, a meatal-based flap is unable to be constructed, a King (1970) type repair would be an alternative. Sometimes, although the meatus has been re-advanced, ventral skin may prove to be insufficient for proper coverage. If so, the penile skin must be widely mobilised with the consideration for a type of skin-plasty such as Byars (1955) flaps. Also, all of our patients had pre-operative administration of testosterone enanthate, which causes temporary genital stimulation and optimises the tissue available for the repeat surgical procedure (Gearhart and Jeffs, 1987).

Lastly, it must be emphasised that the MAGPI procedure is an excellent operation which requires meticulous technique for its high rate of success. As its popularity has increased, however, surgeons have stretched its indications. Therefore, as these 8 patients have shown, this procedure should not be used for the treatment of patients with hypospadias where the meatus lies more proximal than the subcoronal region. When used in this fashion, the risk of meatal regression should be minimised and an excellent result will be obtained.

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Urinary Oestrogen Excretion in Benign Prostatic Hyperplasia and Prostatic Cancer

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Summary—Urinary oestrogen excretion was measured in 20 healthy middle-aged men (controls), in 30 patients with benign prostatic hyperplasia (BPH) and in 32 prostatic cancer (PC) patients. The mean oestradiol (E2) excretion was significantly lower in the PC patients than in the controls and BPH patients. No other significant differences were found in oestrone (E1), oestriol (E3) and total oestrogen (E1+E2+E3) excretion between the 3 groups. The decreased E2 excretion in the PC patients is in accordance with our previous finding concerning significantly lower E2 plasma levels in PC patients. It seems possible that elderly men with lower endogenous oestrogen levels are at higher risk of developing cancer. On the other hand, the age-dependent increased oestrogen levels may play an aetiological role in BPH.

A rise in plasma oestrogen level in men concomitant with increasing age has been reported (Pirke and Doerr, 1973; Bartsch *et al.*, 1977; Rannikko and Adlercreutz, 1983). On the other hand, we have observed significantly higher plasma oestradiol levels in patients with benign prostatic hyperplasia when compared with patients of the same age and body mass who have prostatic cancer (Rannikko and Adlercreutz, 1983). It has been suggested that this difference may play an aetiological role in these diseases.

Results correlating urinary excretion of oestrogens with increasing age and in prostatic diseases are rare and controversial (Owen and Cutler, 1936; Bulbrook *et al.*, 1959; Jönsson *et al.*, 1963; Marmorston *et al.*, 1965; May and Stimmel, 1965; Sköldefors *et al.*, 1976). To our knowledge, no studies have yet been carried out using modern radioimmunological procedures, including a chromatographic step for separation of the oestrogens.

Because it is possible that 24-h urinary output reflects the production of oestrogens more accurately than a simple plasma determination, this study was undertaken to compare oestrogen excretion in normal middle-aged men (controls) and in patients with BPH or PC.

Patients and Methods

The series consisted of 20 normal, healthy, middle-aged men aged between 40 and 59 years (mean 49.4), 30 ambulant patients aged between 51 and 81 years (mean 69.5) with BPH subsequently treated by transurethral resection of the prostate, and 32 ambulant untreated patients aged between 57 and 94 years (mean 71.2) with PC verified by histological or cytological biopsy.

The mean body mass index (BMI) (Gouldbourt and Medalie, 1974) was comparable in all 3 groups, *i.e.* 25.8, 27.5 and 26.0 respectively. None of the subjects had received hormonal therapy before the study. Most were not on any regular medication. None gave a history of liver disease. In 28 cases the PC had metastasised and/or extended locally outside the prostatic capsule. The 4 remaining patients had an intracapsular tumour without metastases.

In many previous studies, subjects with a "normal" prostate based on simple rectal palpation have served as controls. In our opinion, in this particular

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age group, "normal" subjects with regard to the prostatic gland are uncommon and rectal palpation may not reveal symptom-free BPH. In this study, therefore, the BPH patients and the group of younger men served as controls for the PC group.

Hormone analyses were performed on 24-h urine samples before undertaking any surgical procedures. Urinary levels of oestrone (E1), oestradiol (E2) and oestriol (E3) were determined after dilution of the urine sample (reducing the concentration of enzyme inhibitors), enzymatic hydrolysis of the conjugates, and Sephadex LH-20 column chromatography followed by radioimmunoassay (Adlercreutz *et al.*, 1982). Urine (0·3 ml) was diluted with 0·7 ml distilled water and 0·1 ml 1·5 mol/l acetate buffer pH 4·5. The oestrogens were submitted to enzymatic hydrolysis with Helix Pomatia extract, ether extraction by freezing, and chromatography on a Sephadex LH-20 column (0.5 × 0.5 cm in a Pasteur pipette). Radioactive tritiated internal standards of E1, E2 and E3 were added to the urine sample immediately after hydrolysis and losses in the subsequent procedures were corrected, based on recovery values obtained by measuring radioactivity in a small aliquot immediately before radioimmunoassay. The column was prepared and the sample added in 2 × 0·1 ml of the first elution solvent. The eluants were as follows: methanol-toluene 9:91 (v/v) 1.1 ml (discarded), same solvent 1.3 ml (contains oestrone), same solvent 0.4 ml (discarded), same solvent 2.8 ml (contains oestradiol), methanol-toluene 15:85 (v/v) 1.2 ml (discarded) and the same solvent 3.2 ml (contains oestriol). The 3 oestrogen fractions were evaporated to dryness under nitrogen, dissolved in buffer and individual oestrogen concentrations determined by radioimmunoassay using 3 different antisera (anti-E1-carboxymethyloxime-bovine serum albumin, anti-E2-6-carboxymethyloxime-bovine serum albumin (both from Steranti Research Ltd, St Albans), and anti-E3-6-carboxymethyloxime-bovine serum albumin (gift from Dr Kuss)). Oestriol was assayed essentially as described by Göbel and Kuss (1974). In 12 experiments the mean recovery values of non-radioactive conjugated oestrogens added to native urine before hydrolysis, following correction for losses during the procedure, were 106.6, 97.7 and 99.3% for oestrone-3-glucuronide, oestradiol-3-glucuronide and oestriol-16-glucuronide respectively. In 38 experiments, adding to separate duplicate urine samples the oestrogen conjugate and its corresponding free oestrogen before and after hydrolysis, the mean difference in recovery values (lower for the conjugates) were only 1.9, 2.2 and 1.4% for E1, E2 and E3 respectively, indicating that the losses during hydrolysis were minimal. This justified the use of radioactive free oestrogens as internal standards in the method, because radioactive conjugates are not commercially available and were prepared in our own laboratory. The coefficient of variation between assays, calculated from the mean values of duplicates of the control urine pool analysed during a 3-year period ($n = 15$), was 3.7% per oestrone, 5.6% for oestradiol, and 3.5% for oestriol.

The results are expressed as geometric means with standard error ranges. Age is given as an arithmetic mean. Statistical comparisons were made using Student's t test utilising the logarithmic values.

Results

The mean urinary excretion of oestrogens in the 3 groups is presented in the Table. The mean excretion of oestradiol was comparable in control subjects and BPH patients, but significantly lower ($P < 0.025$) in the PC patients. The mean excretion of oestrone was approximately the same in the 3 groups, as was the total mean excretion of oestrogens. The mean excretion of oestriol was highest in the PC patients and lowest in the younger men, but the differences were not statistically significant.

Discussion

In the present study we found the mean urinary excretion of E2 to be significantly lower ($P < 0.025$) in PC patients than in BPH patients of the same age and body mass. This is in accordance with our previous results showing significantly lower mean plasma E2 levels in PC patients compared with BPH patients (Rannikko and Adlercreutz, 1983). The E2 excretion in the PC patients was also significantly lower ($P < 0.025$) than in the younger normal controls. We did not find any significant differences between the BPH patients and the controls. Sköldefors *et al.* (1976) observed a significantly increased oestrogen excretion in patients with BPH when compared with healthy controls, but they did not include any cancer patients in their study.

In contrast to our findings, previous investigators (Owen and Cutler, 1936; Bulbrook *et al.*, 1959; Jönsson *et al.*, 1963) found no difference in oestrogen excretion between controls or BPH patients and PC patients. This may be explained by poor matching of patients and unreliable biological or

Table Urinary Excretion (nmol/24 h) of E1, E2, E3 and E1+E2+E3 in Controls, Patients with BPH and Patients with PC

	E1	*E2*	*E3*	*E1+E2+E3*
Controls (n=20)				
Mean	16.7	13.5	27.2	59.4
SEM-range	15.3–18.2	12.3–14.8	24.8–30.0	55.3–63.9
BPH (n=30)				
Mean	17.2	12.6	32.7	64.4
SEM-range	15.8–18.8	11.7–13.7	30.4–35.2	60.4–68.7
PC (n=32)				
Mean	15.3	10.4	33.4	61.7
SEM-range	13.9–16.9	9.6–11.1	31.1–35.9	58.3–65.2
Significance				
Controls vs BPH	NS	NS	NS	NS
Controls vs PC	NS	$P<0.025$	NS	NS
BPH vs PC	NS	$P<0.025$	NS	NS

NS=not significant.
(Geometric means with standard error ranges).

colorimetric assay methods used in these earlier series. The RIA method used in the present study has been compared with a gas chromatographic/mass spectrometric method (Fotsis and Adlercreutz, 1987) with good correlation of results (unpublished data).

Marmorston *et al.* (1965) and Klosterhalfen *et al.* (1965) demonstrated a shift toward an increased proportion of oestriol excretion in PC patients. We found a similar shift: the mean ratio of E1 plus E2 excretion to E3 excretion was lowest in the PC patients (0·9) compared with the younger controls (1·2) and the BPH patients (1·0), but only the difference between the first 2 groups was significant ($P<0·025$).

The present results, together with our previous findings concerning plasma E2 levels (Rannikko and Adlercreutz, 1983) support the view that endogenous oestrogen may play an aetiological role in prostatic diseases and that elderly men with low oestrogen levels are at higher risk of developing prostatic carcinoma. However, the possibility that the lower oestradiol level is a consequence of the disease itself cannot be excluded.

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The Fate of Testes Following Unilateral Incarcerated Inguinal Hernia in Adult Rats

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Summary—The histological effects of unilateral incarcerated inguinal hernia on the ipsilateral and contralateral testes were examined in adult rats. Three groups were established. In the first group the left testis and caecum were exposed and replaced. In group 2 a left-sided incarcerated inguinal hernia was created with bilateral orchiectomy 24 h later. In group 3 a left-sided incarcerated inguinal hernia was created with reduction after 24 h. The testes of animals in groups 1 and 3 were removed after 15 days. The mean seminiferous tubular diameter (MSTD) and mean testicular biopsy score (MTBS) were determined for ipsilateral and contralateral testes in each of the 3 groups. A decreased MSTD and depressed MTBS, were pronounced in the ipsilateral testes, were found in the testes of group 3 animals. While unilateral incarcerated inguinal hernias caused more pronounced histological changes in the ipsilateral testes, they also affected the contralateral testes, but a time interval was required for the changes to become manifest.

Indirect inguinal hernia is seen in 1 to 2% of men (White and Haller, 1978) and incarceration occurs in 10% of these patients (Condon and Nyhus, 1978). Although the incidence is estimated to be nil in adult patients (Nyhus, personal communication), incarcerated inguinal hernia causes vascular compromise resulting in haemorrhagic infarction of the ipsilateral testis of young children with an incidence of 10 to 15% (Klauber and Sant, 1985). However, unilateral testicular events such as torsion (Nagler and White, 1982), varicocele (Nagler *et al.*, 1985) and undescended testis (Salman *et al.*, 1988), whilst harming the ipsilateral testis, may also cause histological damage to the "normal" contralateral testis and result in diminished fertility.

It is therefore postulated that unilateral incarcerated inguinal hernia can also affect the testes in adults to some extent, and an experimental study was designed to evaluate the effects of unilateral incarcerated inguinal hernia on ipsilateral and contralateral testes in adult rats.

Materials and Methods

The study group comprised 30 adult (60-day-old) male Hacettepe strain albino rats, previously proven to be capable of exhibiting contralateral testicular damage following unilateral torsion following a pilot study on 10 animals. They were maintained in cages of 5 animals with controlled temperature and dark-light cycle. They were supplied with *ad libitum* access to water and rat food.

Surgery was performed through identically opened and closed left abdomino-scrotal incisions employing a sterile technique under general anaesthesia with intraperitoneal instillation of pentobarbital. The animals were randomly allocated to 3 groups:

Group 1. A sham operation was performed on 10 animals with exposure and replacement of the left testis and caecum.

Group 2. Incarcerated inguinal hernias were created in 10 animals. The inguinal canal and external inguinal ring were exposed through a left abdomino-scrotal incision. The caecum was found through the inguinal canal, which remains open throughout life in rats (Kohn and Barthold, 1984). A caecal loop was advanced through the inguinal canal into the scrotum and a size 8 Nelaton's catheter was placed

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in the canal near the caecal loop. The external inguinal ring was narrowed over the caecum and catheter with 4/0 atraumatic silk sutures. The catheter was then carefully removed. The animals were sacrificed after 24 h and both testes were removed.

Group 3. Left-sided incarcerated inguinal hernias were created in 10 animals as described above, but the hernias were surgically reduced through the same incisions 24 h later. The animals were followed up for 15 days.

All animals, except those in group 2 which were sacrificed after 24 h, were sacrificed after 15 days. Both testes were removed, placed in Bouin's solution and embedded in paraffin blocks. Sections were cut and stained with haematoxylin and eosin. Testicular biopsies were studied blind and in random order by a pathologist. The 25 most circular tubules were identified in each testicular biopsy section and the diameters measured with a 10 × objective and a micrometer ocular. The mean seminiferous tubular diameter (MSTD) was determined for each testis. Germinal epithelium maturity was graded using a modified Johnsen testicular biopsy score (Salman *et al.*, 1988). By using 40 × objective, 25 tubules were evaluated and given a score from 1 to 10 according to the criteria show in Table 1. The mean testicular biopsy score (MTBS) was calculated for each testis.

Table 1 Testicular Biopsy Scores*

Score	*Description*
10	Complete spermatogenesis with many spermatozoa
9	Only few spermatozoa (5/tubule)
8	No mature spermatozoa, but late spermatids (differentiation to form spermatozoa)
7	Many spermatids without differentiation
6	Only few spermatids (5/tubule)
5	Many spermatocytes
4	Only few spermatocytes (5/tubule)
3	Only spermatogonia
2	Sertoli cells without germ cells
1	No cells

*If germinal epithelium was disorganised with sloughing or obliteration of the lumen, a lower score was given.

Statistical comparisons were made between biopsies from each group of rats using the Mann-Whitney U test, and P values less than 0.05 were considered to be significantly different.

Results

An animal from group 1 died of an unknown cause; 9 animals in group 1 and 10 animals each in groups 2 and 3 were available for evaluation after sacrifice.

The MSTD and MTBS are summarised in Table 2. The MSTD of the right and left testes in groups 1, 2 and 3 revealed no significant difference. While the difference between the MSTD of ipsilateral testes in groups 1 and 2 was not significant, the MSTD of testes in group 3 differed significantly compared with the ipsilateral testes in groups 1 and 2. The MTBS of the right and left testes in group 2 showed no significant variation, but right and left testes in groups 1 and 3 differed significantly. The variation between the MTBS of ipsilateral testes in groups 1 and 2 was not significant, but the testes in group 3 differed significantly when compared with the ipsilateral testes in groups 1 and 2 (Figs 1, 2 and 3).

Discussion

Testicular histological changes and a subsequent decrease in fertility after unilateral testicular events such as torsion (Krarup, 1978; Nagler and White, 1982), varicocele (Nagler *et al.*, 1985; Nagao *et al.*, 1986) and undescended testis (Salman *et al.*, 1988; Kogan, 1985) have previously been reported, but to the best of our knowledge this is the first experimental study of the testes after unilateral incarcerated inguinal hernia.

Ipsilateral testicular atrophy is reported to occur 15 days after manipulation of the spermatic cord

Table 2 Summary of Mean Seminiferous Tubular Diameters and Mean Testicular Biopsy Scores

	Mean seminiferous tubular diameter (microns ± SE)		*Mean testicular biopsy score (X ± SE)*	
Groups	*Right testes*	*Left testes*	*Right testes*	*Left testes*
1	268.33 ± 2.08	263.55 ± 3.22	9.96 ± 0.02	9.56 ± 0.14
2	264.79 ± 2.33	261.00 ± 8.64	9.62 ± 0.06	9.31 ± 0.34
3	208.90 ± 18.8	207.90 ± 19.8	7.99 ± 0.89	5.65 ± 1.09

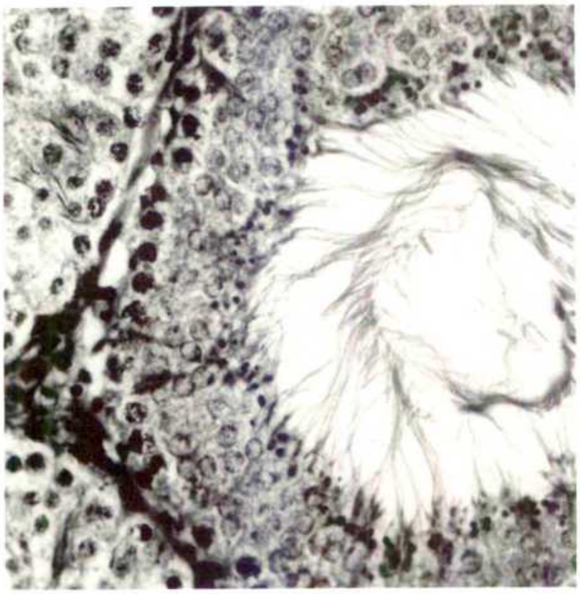

Fig. 1 Contralateral testis from group 1 demonstrating normal spermatogenesis. (H and E × 300).

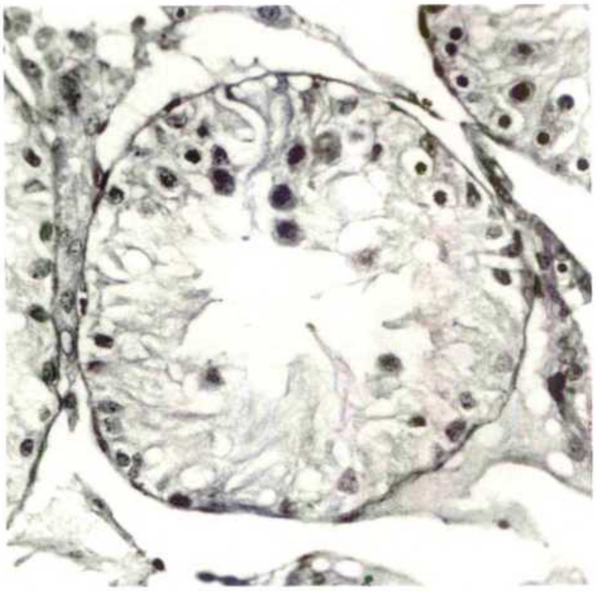

Fig. 2 Ipsilateral testis from group 3 showing decrease in number of germ cells and tubular diameter. (H and E × 300).

(Madarikan, 1987). Manipulating the left testis and caecum also affected spermatogenetic activity in the left testes compared with the contralateral testes in our experimental design, but the MSTD remained unaltered and germinal epithelium maturity was well preserved. On the other hand, our experimental model did not reveal significant differences between the right and left testes, or between the ipsilateral controls with the utilised parameters after 24 hours' incarceration. Contrary to the findings after 24 hours' incarceration, damage consisting of decreased MSTD and depressed MTBS, more prominent in the ipsilateral testis, was encountered in both ipsilateral and contralateral testes 15 days after reducing a unilateral incarcerated inguinal hernia. While unilateral incarcerated inguinal hernia caused more pronounced histological changes in the ipsilateral testis, it also affected the contralateral testis, but a time interval similar to that encountered in contralateral testicular damage following unilateral testicular torsion (Nagler and White 1982) was required for any deterioration to become manifest.

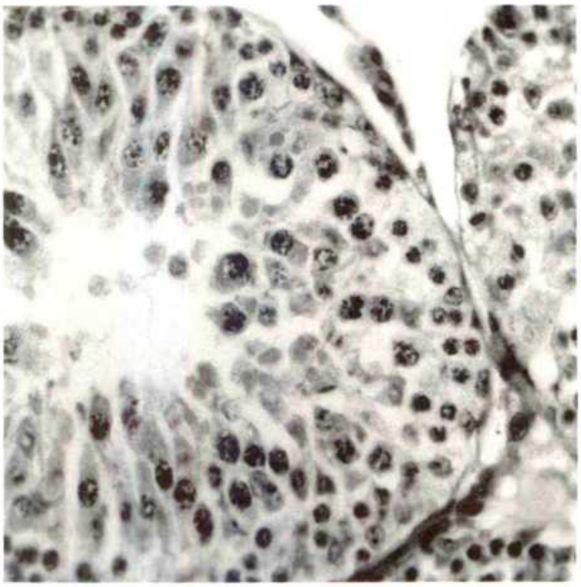

Fig. 3 Contralateral testis from group 3 showing deterioration. No spermatids or spermatozoa are present despite the presence of abundant cells in division. (H and E × 300).

Unilateral incarcerated inguinal hernia may result in bilateral testicular deterioration. Fertility following unilateral incarcerated inguinal hernia requires further study.

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Prostaglandin 15-hydroxydehydrogenase Activity in Human Penile Corpora Cavernosa and its Significance in Prostaglandin-mediated Penile Erection

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Summary—Prostaglandins may be involved in human penile erection and erectile failure. To evaluate the possible role of prostaglandin metabolism in the penile tissue, the activity of nicotinamide adenine dinucleotide-dependent prostaglandin 15-hydroxydehydrogenase was assayed in the corpora cavernosa of the human penis. Km values (mean ± SD) of the enzyme for PGE_1, PGE_2 and $PGF_{2\alpha}$ were 60.1 ± 4.2, 17.7 ± 1.5 and 16.1 ± 1.2 μM respectively; Vmax values (mean ± SD) were 0.219 ± 0.062, 0.510 ± 0.012 and 0.424 ± 0.007 nmol/min/mg protein respectively. The implications of these findings in the erectile process are discussed.

The intracavernous injection of prostaglandin $(PG)E_1$ has been reported to produce penile erection in man (Virag and Adaikan, 1987). This prostaglandin has been the subject of clinical trials for the management of impotence. It relaxes the corpus cavernosum of the human penis (Adaikan, 1979) and inhibits the alpha-adrenergic neurotransmission which is essential for the maintenance of a flaccid and non-erectile state of the penis (Adaikan and Ratnam, 1987). These results suggest that PGE_1 may be involved in the biochemical process of erection. Thus the regulation of tissue levels of PGE_1 may be important in penile erection.

Effective tissue concentrations of prostaglandins depend primarily upon the rate of synthesis, release and subsequent degradation in the tissue. It has already been shown that the corpora cavernosa of the human penis have the ability to synthesise various prostaglandins *in vitro* (Roy *et al.*, 1984; Jeremy *et al.*, 1986). It is known that prostaglandin 15-hydroxydehydrogenase (PGDH, E.C. 1.1.1.141), a soluble cytoplasmic enzyme, catalyses the initial reaction in the metabolic degradation of prostaglandins to inactive 15-keto metabolites (Hansen, 1976). We present new evidence for the presence of significant PGDH activity in the corpora cavernosa of the human penis and discuss the possible implications of these findings in the erectile process.

Materials and Methods

A macroscopically normal penis was obtained from each of 15 trans-sexual subjects undergoing sex change operations at the National University Hospital. After collection, each tissue specimen was immediately dissected and washed thoroughly with chilled physiological saline. The corpora cavernosa were homogenised gently at 0° to 4°C with a Teflon hand homogeniser in 3 volumes of Tris-HCl buffer (50 mM, pH 8.0) containing 50 mM sucrose, 5 mM dithiothreitol and 1 mM EDTA. The homogenate was centrifuged at 100,000 g for 60 min (0°–4°C) and the cytosolic supernatant was used immediately.

Prostaglandin 15-hydroxydehydrogenase activity was assayed using a spectrophotometric method in which NADH or NADPH formation is measured (Hansen, 1976). The incubation medium contained 50 mM Tris-HCl buffer (pH 8.0), 2 mM NAD^+ or $NADP^+$, 0.04–0.8 mM PGE_1, PGE_2 or $PGF_{2\alpha}$ (in ethanol), 1 mM dithiothreitol and 0.4 ml cytosolic supernatant (protein concentration 4–5 mg/ml) in a final volume of 2.5 ml. The final concentration of

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ethanol was less than 2% and had no effect on PGDH activity. The reaction was initiated by the addition of cytosolic protein and carried out at 37°C for 30 min. The increase in the extinction for the formation of NADH or NADPH was measured at 340 nm in a Hewlett Packard 8451A diode array spectrophotometer. PGDH activity was corrected for non-specific formation of NADH or NADPH in the presence of NAD^+ or $NADP^+$ but in the absence of PGs. Protein concentration was estimated according to the method of Lowry *et al.* (1951), using bovine serum albumin (BSA) as the standard. All reagents were of analytical grade and obtained from Sigma Chemical Co., USA. The enzyme activity is expressed as amounts of 15-keto metabolites formed from the substrates in nmol/min/mg protein of the cytosolic fractions at 37°C. Km and Vmax values for the enzyme were computed by linear regression of Lineweaver-Burk equations (Dixon and Webb, 1964) using VisiCal (Personal Software, Inc.). Correlation coefficients were at least 0.999. The data were analysed by an unpaired Student's *t* test (two-tailed) with a P value < 0.05 considered statistically significant.

Results

The Table shows the results of kinetic studies of PGDH activity in the cytosolic fractions of corpora cavernosa of the human penis using NAD^+ as cofactor and PGE_1, PGE_2 and $PGF_{2\alpha}$ as separate substrates. There was no $NADP^+$-dependent PGDH activity in the tissue samples studied. As judged by the Km value, which is the reciprocal of enzyme-substrate affinity (Dixon and Webb, 1964), it appears that the affinity of PGE_2 for the enzyme was similar to that of $PGF_{2\alpha}$ ($P > 0.3$) but was much higher than that of PGE_1 ($P < 0.001$). Hence, as indicated by the Vmax values, the rate of metabolic degradation by the enzyme of both PGE_2 and $PGF_{2\alpha}$ was much higher than that of PGE_1 ($P < 0.001$).

Table NAD^+-dependent Prostaglandin 15-hydroxydehydrogenase Activity in the Corpora Cavernosa of the Human Penis

Substrate	*Km (μM)*	*Vmax (nmol/min/mg protein)*
PGE_1	60.1 ± 4.2*	0.219 ± 0.062**
PGE_2	17.7 ± 1.5†	0.510 ± 0.012††
$PGF_{2\alpha}$	16.1 ± 1.2‡	0.424 ± 0.007‡‡

* vs†, $P < 0.001$; * vs‡, $P < 0.001$, † vs‡, $P > 0.3$
** vs††, $P < 0.001$; ** vs‡‡, $P < 0.001$, †† vs‡‡, $P > 0.2$
Each value is the mean ± SD of at least 5 duplicate experiments

Discussion

At the penile level, the neuromuscular and vascular reflexes leading to relaxation of the corpus cavernosum and vascular smooth muscle of the penis are essential in the process of penile tumescence and erection. As stated above, PGE_1 potently relaxes the penile muscle (Adaikan, 1979) and also inhibits the adrenergic activity in the corpus cavernosum muscle (Adaikan and Ratnam, 1987). This phenomenon is believed to be essential in the mechanism of erection (Adaikan and Ratnam, 1987). In contrast, however, the penile smooth muscle is contracted by $PGF_{2\alpha}$, causing muscle tone to increase and initiating rhythmic activity. Prostaglandin E_2 produces muscle contraction at low doses and relaxation at high doses (Adaikan, 1979). From the present study, it would appear that human penile PGDH activity, which differentially inactivates PGE_1, PGE_2 and $PGF_{2\alpha}$, may play a significant role in the regulation of penile erection by controlling the tissue levels of PGs. The observation that PGE_1, when given intracavernously to patients, does not produce pharmacologically-induced prolonged erection or priapism (Virag and Adaikan, 1987) could be attributed to the PGDH activity in the cavernosa.

The penile tissue used in this study was collected from trans-sexual patients receiving oestrogen therapy for the management of male-to-female trans-sexualism. The plasma testosterone levels in these patients were less than 1 ng/ml. There is evidence to suggest that oestrogen treatment increases PGDH activity in the uterus of ovariectomised rats (Alam *et al.*, 1976; Kogo *et al.*, 1984; Franchi *et al.*, 1985) but decreases the enzyme activity in the kidney (Blackwell and Flower, 1976; Cagen *et al.*, 1985). However, it is not known whether variations in oestrogen and testosterone levels have any effect on PGDH activity in the penile tissue in animal models. This is an area that deserves further study.

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Penile Venous Drainage in Erectile Dysfunction. Anatomical, Radiological and Functional Considerations

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Summary—To elucidate further the penile venous anatomy and its role in the haemodynamics of erection, we performed pharmacological cavernometry and cavernography in 95 patients with venogenic impotence and in 12 patients with psychogenic impotence. The findings were correlated with those of dissection in 10 adult male cadavers. Cavernography confirmed that the main venous drainage of the corpora cavernosa is via the cavernous veins, with additional drainage through the crural, circumflex and deep dorsal veins and demonstrated that, in patients with venogenic impotence, the cavernous veins are the common site of leakage.

Cavernometry provided valuable parameters for the quantification of the degree of venous leakage. Detailed knowledge of the penile venous system and cavernometry and cavernography are essential for the proper diagnosis and treatment of patients with venogenic impotence.

The role of the penile veins in the mechanism and haemodynamics of erection has long been a matter of controversy. At the beginning of the century, Wooten (1902) and Lydston (1908) reported the importance of penile venous drainage in erection and the temporary restoration of potency after ligation of the deep dorsal vein. Despite these early reports, the debate continued as to whether venous outflow restriction occurs during erection. The controversy was based on the conflicting results from the human penile perfusion studies of Newman and Reiss (1984) and the xenon-133 washout studies of Shirai *et al.* (1978) and Wagner and Uhrenholdt (1980). Recent haemodynamic studies have clearly shown that venous outflow restriction occurs during erection and that a normal venous closure mechanism is essential not only for initiating but also for maintaining erection (Lue *et al.*, 1983, 1984; Juenemann *et al.*, 1986; Fournier *et al.*, 1987). With the realisation of the importance of the penile venous drainage system in erection and the frequency of venous incompetence as a cause of organic impotence, Ebbehoj *et al.* (1980) and Wagner (1981) popularised cavernography during visual erotic stimulation as a method for diagnosing venous leakage. Virag (1982) and Wespes *et al.* (1984, 1986) subsequently proposed dynamic cavernography with saline-induced erection. Recently Lue *et al.* (1986, 1987) reported the ease of performing dynamic cavernometry/cavernography after erection induced by vasoactive drugs.

Because the penile venous system had been understood only superficially and often inaccurately, we dissected the penile veins in 10 adult male cadavers and correlated these anatomical findings with the results of pharmacocavernometry and cavernography in patients with venogenic impotence. We believe that this systematic knowledge of the detailed anatomy of the penile veins, combined with quantification of the amount of venous leakage by cavernometry and localisation of the site of the leakage by cavernography, will be of great value in the diagnosis and surgical treatment of venogenic impotence.

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Materials and Methods

Anatomical dissection of penile veins in human cadavers

Penile veins were dissected in 10 formalin-preserved adult male cadavers (in whom the exact age, erectile status and cause of death were unknown). The technique, performed with magnifying glasses and microsurgical instruments, is summarised briefly as follows. The skin and superficial fascia (Colles' fascia) of the penis and lower abdomen were completely excised, exposing the superficial penile veins and their main draining vessels. Buck's fascia was incised longitudinally and both edges were reflected laterally down to the ventral surface of the penis, exposing the deep dorsal vein and its tributaries. For proximal dissection of the deep dorsal vein, the penis was freed by cutting the suspensory ligament as well as the crural attachment to the ischial bones. An H-shaped segment of pubic bone was removed with a Gigli saw. The deep dorsal vein was dissected completely, both distally to the glans and proximally to its termination into the periprostatic plexus. For exposure of the cavernous veins, the dorsal artery and nerve were retracted laterally. The cavernous veins were then dissected from the region of the hilum of the penis to their drainage into the internal pudendal vein. All penile veins were excised, opened longitudinally and examined under the dissecting microscope.

Functional and radiological evaluation of penile veins

Pharmacological cavernometry and cavernography were performed in 107 patients, divided into 2 groups.

Group I (control) consisted of 12 patients with the typical findings of psychogenic impotence.

Group II consisted of 95 patients with venogenic impotence. The suspicion of a venous origin was based on their inability to achieve or maintain a good erection despite an excellent arterial response to the intracavernous injection of papaverine as demonstrated by pulsed Doppler analysis and high-resolution ultrasonography (Lue *et al.*, 1985).

For cavernometry and cavernography, performed under aseptic conditions, a 21 gauge butterfly needle was inserted into each corpus cavernosum. One needle was connected to an arterial pressure monitor and the other to a perfusion pump. A rubber band was placed snugly at the base of the penis and 60 mg of papaverine were injected into either line. The rubber band was kept in place for 2 min to prevent rapid leakage into the systemic circulation. Changes in the intracavernous pressure were monitored continuously. If the pressure remained below 80 mm Hg (venous closure pressure) 12 min after injection of papaverine, tumescence was then augmented by gradual infusion of normal saline into one corpus cavernosum, starting at a rate of 5 ml/min with gradual increases (to 15, 30, 45, 60, 75 and 100 ml/min) until either the intracavernous pressure increased above 80 mm Hg or the 100 ml/min rate had been delivered. When the pressure reached 80 mm Hg or more, the infusion rate was gradually decreased to determine the rate required to maintain the intracavernous pressure at 80 to 90 mm Hg (maintenance flow rate).

The infusion was then stopped, the intracavernous pressure monitored for an additional 5 min, the drop in intracavernous pressure was calculated as a percentage of the maximum, and a curve was plotted. The pressure was then restored to 80 mm Hg or higher, if possible, while maintaining the infusion rate at a level not exceeding 100 ml/min. Diluted contrast material (1:1 with saline; total volume 60–120 ml) was injected for X-ray visualisation of the site of venous leakage. X-ray films were taken with the patient in the supine and 45° oblique positions.

Results

Anatomical dissection

Three systems of veins drain the penis (Table 1).

The superficial venous system consists of multiple subcutaneous veins that unite at the root of the penis to form the superficial dorsal vein. This drains

Table 1 Anatomy of the Penile Venous System in 10 Cadavers

Superficial venous system (superficial dorsal vein)		
	Single trunk in 7	
	Two trunks in 3	
Drainage	Left saphenous vein alone in 6	
	Right saphenous vein alone in 1	
	Both saphenous veins in 3	
Intermediate venous system		
	Range	Average
No. of veins forming the retro-coronal plexus	5–8	6.6
No. of deep dorsal veins	1–3	1.7
No. of circumflex veins	3–10	5.8
Deep venous system		
No. of branches forming the cavernous vein	2–5	3.4
No. of crural veins	3–5	4

into the left saphenous vein, the right saphenous vein, or both.

The intermediate drainage system consists of the deep dorsal vein and the circumflex veins. The deep dorsal vein runs on the dorsal surface of the penis deep to Buck's fascia in a groove between the two corpora cavernosa. It then passes under the pubic arch between the two layers of the suspensory ligament to drain into the periprostatic plexus. The circumflex veins are narrow venous channels present only in the distal two-thirds of the penis. They arise from the undersurface of the corpus spongiosum and course around the lateral surface of the corpus cavernosum to open obliquely into the deep dorsal vein. Among the 10 cadavers, their number ranged from 3 to 10.

The deep venous system consists of the cavernous and crural veins. The cavernous veins (Fig. 1) are thin-walled large veins arising from the dorsomedial surface of each corpus cavernosum in the region of the hilum at the junction of the middle and proximal thirds of the penis. These veins unite to form 1 to 2 main cavernous veins that run proximally as the most medial and deep structure, with cavernous arteries and nerves superficial and lateral to them, to drain into the internal pudendal veins. A large venous connection was consistently seen between the cavernous veins and the periprostatic plexus. In addition, in 4 cadavers 1 to 2 accessory cavernous veins were seen emerging from the dorsolateral surface of the proximal half of the penis and draining into the periprostatic plexus.

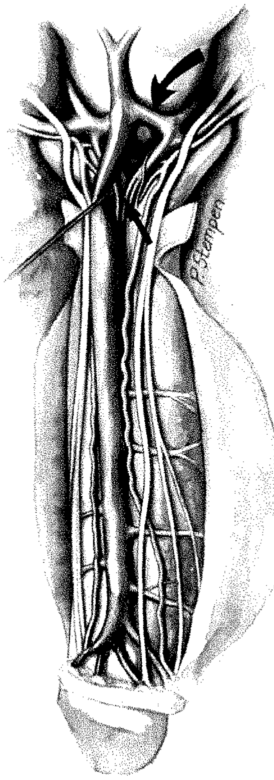

Fig. 1 Deep dorsal vein (retractor) with the cavernous veins evident underneath (arrow). The communication between the intermediate and deep venous systems is shown at the curved arrow.

Multiple tiny veins (crural veins) were seen emerging from the dorsomedial surface at the crus of the penis. These joined together to form a larger venous channel running proximally under the ischial bone to drain into the internal pudendal vein.

Cavernometry

Four values were considered in the functional evaluation of the penile venous system: the infusion flow rate necessary to achieve full erection (induction flow, IF); the rate necessary to maintain erection (maintenance flow, MF); the maintenance index (MI = MF/IF); and the drop in intracavernous pressure 5 min after stopping the infusion, calculated as a percentage of the maximal pressure.

According to these measurements, patients were classified into 4 groups (Table 2, Fig. 2) depending upon the degree of venous leakage and the competence of the venous closure mechanism: 12 patients (*i.e.* those with psychogenic impotence) had normal results; 14 had mild impairment of the closure mechanism; 29 had moderate venous leakage; and 52 had severe venous leakage. In fully one-half of the last group (26), erection was never attained, even with the highest infusion rate (100 ml/min). Their average maximal intracavernous pressure was 27.7 mm Hg.

Cavernography

In the 12 patients with psychogenic impotence, papaverine injection resulted in tumescence only; however, the addition of a small amount of diluted contrast material resulted in full erection. Cavernography in this group showed complete filling of both corpora cavernosa with minimal visualisation (or none) of the cavernous or deep dorsal vein (Fig. 3). Accordingly, the venous closure mechanism was considered normal.

Because our findings at dissection demonstrated 3 venous drainage systems, venous leakage may conceivably occur through any one or a combination. In the 95 patients with venogenic impotence,

Table 2 Results of Cavernometry in 107 Patients

Group	*No. of patients*	*Induction flow (ml/min)*	*Maintenance flow (ml/min)*	*Maintenance index*	*% drop in intracavernous pressure* 0.5	1	2	3	4	5 (min)
Normal	12	35	4.98	0.124	4.6	21.5	28.5	42.3	46.1	47.6
Mild leak	14	37	11.3	0.31	21.1	38.6	46.3	66.5	73	77
Moderate leak	29	42.7	17.1	0.41	29.6	53.3	66.1	74.9	77.6	78
Severe leak	52	70	63.5	0.90	67.7	79	81.8	79.4	79.4	80

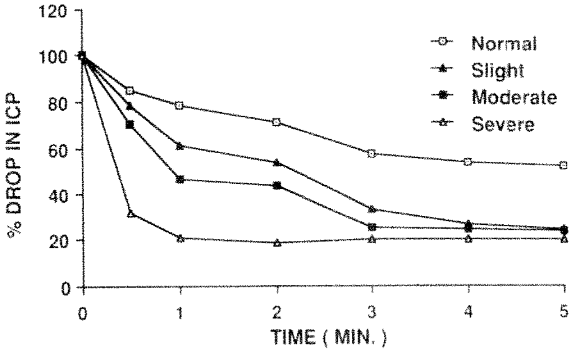

Fig. 2 The percentage drop in intracavernous pressure after cessation of papaverine infusion permitted classification of the degree of the patients' venous leakage.

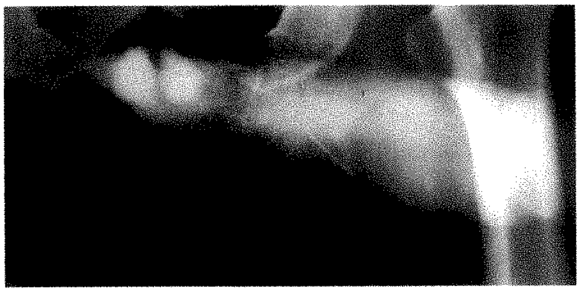

Fig. 3 Cavernography in a control subject demonstrated complete filling of both corpora cavernosa and non-visualisation of veins.

cavernography enabled classification according to drainage system.

Leakage into the superficial venous system (Fig. 4A) encompassed leakage into the superficial dorsal veins, the superficial veins on the lateral and ventral penile surface, the scrotal veins and pampiniform plexus (Fig. 4B) and leakage into their draining veins (external pudendal and saphenous). Of the 51 patients so classified (53.7%), 6 (6.3%) showed leakage into the superficial venous system only, whereas, in the remainder, leakage into other venous systems coexisted: 11 into the intermediate venous system; 3 into the glans and/or corpus spongiosum (Fig. 5); 7 into the deep venous system; and 24 (25.3%) demonstrated massive leakage into all 3 venous systems (Table 3).

Leakage into the intermediate venous system encompassed leakage into the deep dorsal vein and glans penis and their draining periprostatic and perivesical plexuses (Fig. 6). This was shown in 67 patients (70.5%), either alone (9 patients, 9.5%) or in combination with superficial and/or deep venous leakage (58 patients, 61.1%) (Table 4).

Leakage into the deep venous system (Fig. 7A)

Table 3 Venous Leakage Through the Superficial System

	No. of patients	*% of total*
Incidence	51	53.8
Leakage through superficial system only	6	6.3
Leakage through superficial system and other systems	45	67.5
Sup. and deep dorsal vein	11	11.6
Sup. and glans/corpus spongiosum	3	3.2
Sup. and cavernous vein	7	7.6
All 3 systems	24	25.3

Table 4 Leakage Through the Intermediate Venous System

	No. of patients	*% of total*
Incidence	67	70.5
Leakage through intermediate system only	9	9.5
Leakage through intermediate and other systems	58	61.1
*Deep dorsal vein and superficial	11	11.6
Deep dorsal and cavernous	23	24.2
All 3 systems	24	25.3

* Leakage into the glans/corpus spongiosum was associated with superficial system leakage in 3, with deep dorsal vein leakage in 6.

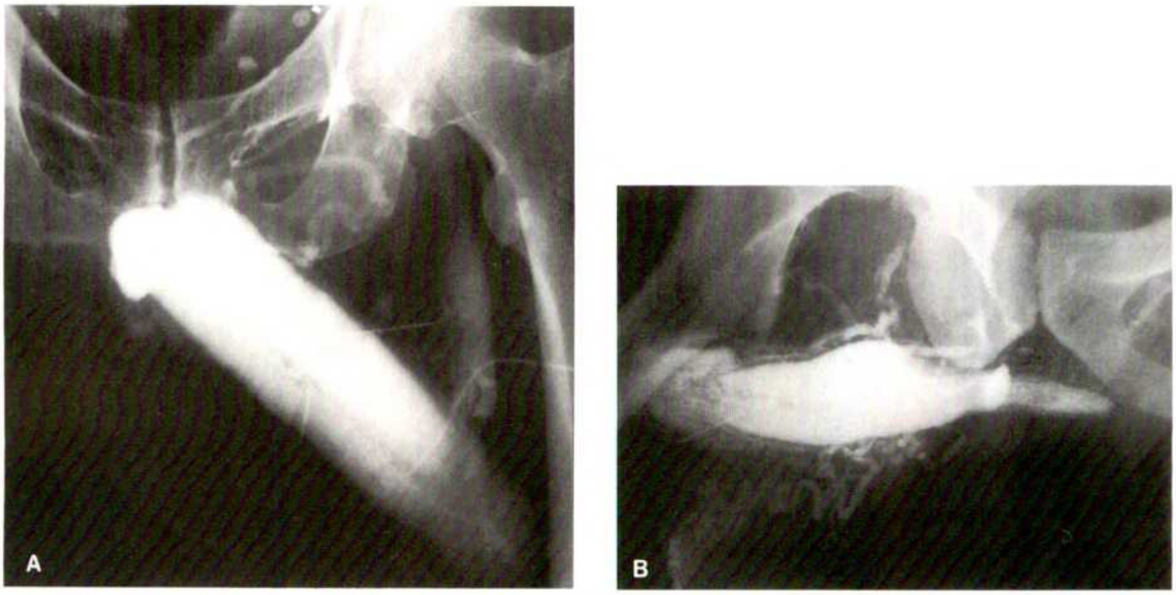

Fig. 4 Leakage through the superficial venous system. (A) Drainage from the superficial dorsal vein into the left saphenous vein. (B) Leakage into the scrotal veins.

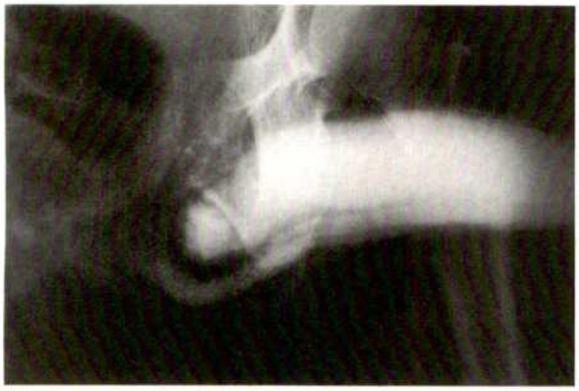

Fig. 5 In this patient with superficial venous leakage, cavernography demonstrated leakage into the corpus spongiosum also.

encompassed leakage into the cavernous and crural veins and their draining internal pudendal veins. Leakage into the deep venous system was seen in 70 patients (73.7%): in 15 (15.8%) through the cavernous veins only; in only 1 (1.1%) through the crural veins exclusively (Fig. 7B); in the remaining 54 (56.8%), deep venous leakage was combined with leakage into other systems (Table 5, Fig. 8).

The fact that our dissection consistently showed a connection between the periprostatic plexus and the cavernous veins can explain the visualisation of any of them through the leakage into either the deep dorsal or cavernous veins.

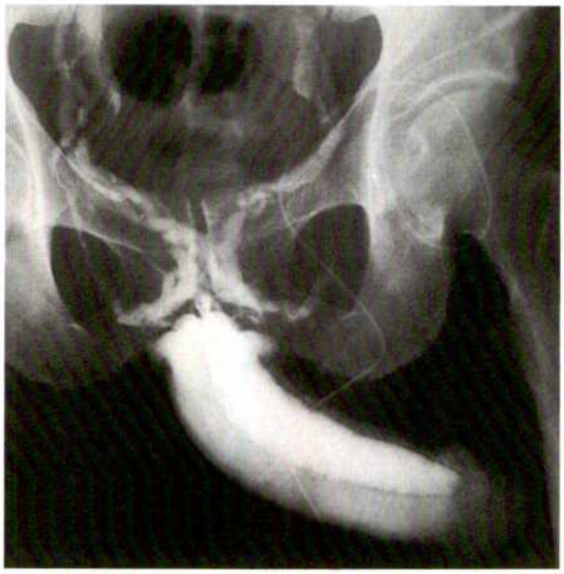

Fig. 6 Intermediate venous system leakage. Note visualisation of the glans, deep dorsal vein, periprostatic plexus and internal pudendal vein.

Discussion

Occlusion of the penile veins is one of the most important haemodynamic events for both initiating and maintaining erection, yet the mechanism of occlusion has long been conjectural. Scanning electron microscopic studies of corrosion casts of

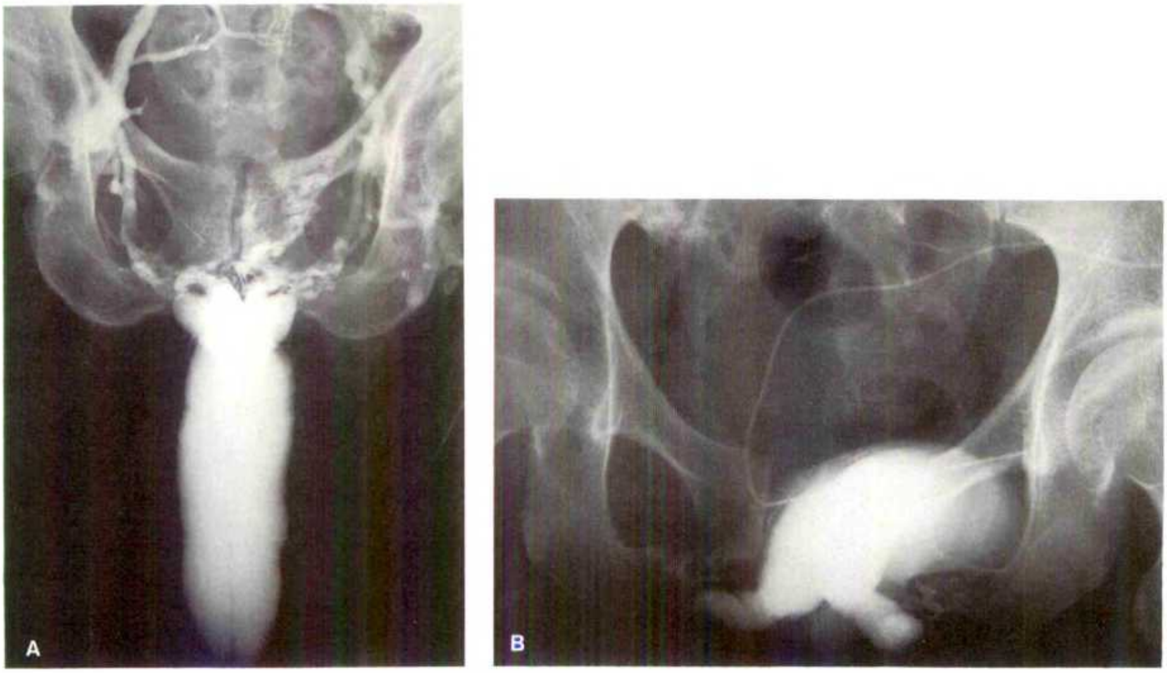

Fig. 7 Deep venous system leakage. (A) Leakage into the cavernous vein and through it into the internal pudendal vein and periprostatic plexus. (B) Leakage through the crural veins.

the human and canine penis (Fournier *et al.*, 1987) have demonstrated that the sinusoidal system empties into an extensive subtunical venular plexus. The unique position of these venules allows them to be compressed during erection between the dilated sinusoids and the non-compliant tunica albuginea, thus reducing venous outflow. Multiple emissary veins arise from this subtunical plexus to traverse the tunica albuginea obliquely and drain, in the distal two-thirds of the penis, into the circumflex veins and, in the proximal third, into the cavernous veins.

Accordingly, venous leakage may result either from a defect in the sinusoidal smooth muscles, preventing efficient sinusoidal distension and venous occlusion, or from a primary defect in the development of the subtunical venular plexus. In addition, venous leakage may also occur through abnormal drainage (*i.e.* an ectopic or aberrant vein) of the corpora cavernosa (Virag, 1982).

Table 5 Leakage Through the Deep Venous System

	No. of patients	*% of total*
Incidence	70	73.7
Leakage through cavernous veins only	15	15.8
Leakage through deep and other systems	54	15.8
Cavernous and deep dorsal veins	23	24.2
Cavernous and superficial	7	7.4
All 3 systems	24	25.3
Leakage through the crural veins only	1	1.1
Crural and cavernous leakage	33	34.7

Dissection of the penile veins has shown that the superficial venous system provides the main drainage to the skin and fascial coverings of the penis, and not to the glans penis as has been previously

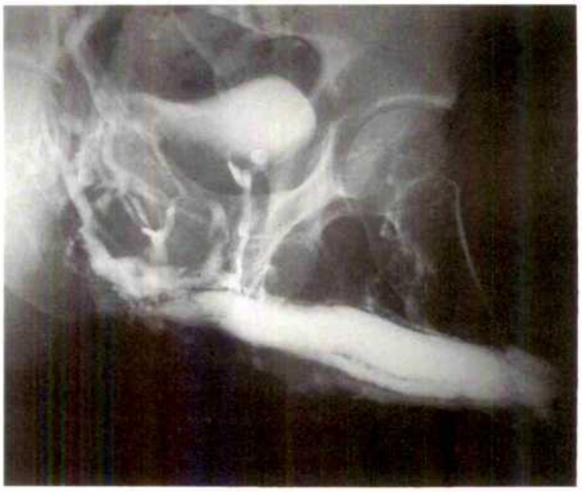

Fig. 8 Cavernography demonstrating leakage into all 3 systems.

Table 6 Classification of Venous Leakage based on Cavernometric Results

		% drop in intracavernous pressure		
Category	*Maintenance flow (ml/min)*	*0.5*	*1 (min)*	*2**
Normal	<10	<25	<30	<40
Mild	10–15	<25	30–40	40–50
Moderate	15–30	25–45	40–70	50–70
Severe	>30	>45	>70	>75

* Values beyond 2 min are largely confirmatory.

reported (Fitzpatrick, 1975). These veins drain mainly into the external pudendal and saphenous veins. In all 10 cadavers, no abnormal veins were seen draining the corpora cavernosa directly into the superficial venous system. However, cavernography clearly demonstrated leakage from the corpus cavernosum directly into the superficial venous system through abnormal veins in 6 of our 95 patients.

The intermediate venous system, consisting of the deep dorsal and circumflex veins, provides the venous drainage of the glans and corpus spongiosum urethrae and contributes to the drainage of the distal two-thirds of the corpora cavernosa. A connection between the deep dorsal vein and the superficial venous system was found in 7 of the 10 cadavers. This communication might explain the simultaneous visualisation of both systems seen in 11 of our 95 patients. Leakage into the glans penis and/or corpus spongiosum was seen in 9 patients. This might be due either to retrograde flow through the deep dorsal vein as a result of incompetent valves or to an abnormal communication with the corpus cavernosum as first described by Ebbehoj *et al.* (1980).

Dissection of human cadavers has clearly shown that the main venous drainage of the corpora cavernosa is via the cavernous veins with additional drainage through the crural veins. As the cavernous veins provide the main drainage of the corpora cavernosa, they are considered to be the main site of venous leakage (Padma-Nathan and Goldstein, 1987). Our anatomical findings correlated well with the radiological findings, where leakage through the cavernous veins was found in 70 patients (73.7%) either alone or in combination with leakage through other venous systems. In all cadavers, connections were found between the cavernous veins and the periprostatic plexus; however, a communication between the deep dorsal vein and cavernous veins was not seen.

At dissection, crural veins were seen as tiny veins draining the crura of the penis. These were visualised in association with cavernous vein leakage in 33 of our patients, but as the sole site of leakage in only 1 patient. They emerge from the dorsolateral surface of the crus and thus are best demonstrated radiologically in the oblique position. Accordingly, crural ligation, which has been described as a method for treating venous leakage (Bar-Moshe and Vandendris, 1987), will not be sufficient in most cases as it will not correct leakage through the cavernous veins. In addition, this technique might endanger the penile artery, which traverses in close proximity to the crus of the penis.

Dynamic cavernometry as a method of functional evaluation of penile veins and quantification of the amount of venous leakage was first described by Virag *et al.* (1984), who measured the rate of saline perfusion required to achieve and maintain artificial erection. However, this method has been considered non-physiological, as in some cases flow rates as high as 250 ml/min could not produce erection (Newman and Reiss, 1984). In addition, this amount of fluid may not be well tolerated by patients with cardiovascular problems. Cavernometry after intracavernous injection of vasoactive drugs, described by Lue *et al.* (1986), is simpler, more physiological and safer. With this method, the flow rate necessary to induce erection can be reduced from 133 ml/min (the study of Virag *et al.* (1984)) to 35 ml/min, and the mean flow rate needed to maintain erection can also be reduced (from 41 to 50 ml/min reported by Virag *et al.* (1984) and Buvat *et al.* (1986), respectively) to 5 ml/min.

Dynamic pharmacocavernometry enabled us to quantity the amount of venous leakage and classify it as mild, moderate or severe. Although our rates of induction and maintenance flow were different from those reported by Virag and Buvat, who did not use papaverine, our maintenance index was similar to Virag's.

The induction flow rate has little diagnostic value as it is dependent on individual penile size. Indeed, in our study there was no significant difference between the induction rate in controls (the 12 patients with psychogenic impotence) and in those with mild and moderate venous leakage. It is valuable only in those patients with severe venous leakage in whom no erection can be achieved and consequently no other measurement can be obtained, as was the case in 26 of 52 patients with severe leakage. In contrast, the maintenance flow rate and the drop in intracavernous pressure provided more accurate information about the quantity of venous leakage. This latter value was significantly different in all groups (Fig. 2). Based on our cavernometry results in 107 patients, the parameters shown in Table 6 are most useful for quantifying the amount of venous leakage.

In conclusion, awareness of the venous drainage of the penis, based on anatomical knowledge, coupled with dynamic pharmacocavernometry and cavernography, will improve the selection of treatment and the results obtained in patients with venogenic impotence.

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Penile Response to Intracavernosal Vasoactive Intestinal Polypeptide Alone and in Combination with Other Vasoactive Agents

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Summary—Intracavernosally injected vasoactive intestinal polypeptide (VIP) (2 μg and 4 μg) resulted in penile tumescence even in men with predominantly organic impotence. Papaverine and phentolamine were successful in inducing erections in all subjects studied but the addition of VIP to this combination improved the erectile response further. A combination of papaverine and VIP produced penile rigidity similar to that with papaverine and phentolamine.

While intracavernosal VIP alone produced disappointing penile responses, its combination with papaverine potentiated the response to this drug, probably by increasing venous outflow resistance.

Vasoactive intestinal polypeptide has been found in high concentration in the erectile tissue of the human penis (Polak *et al.*, 1981). It has been suggested that this peptide either modulates or acts as the neurotransmitter mediating the erectile response at the non-adrenergic, non-cholinergic, post-ganglionic terminals of the parasympathetic supply to the penis (Anderson *et al.*, 1983; Adaikan *et al.*, 1986).

Ottesen *et al.* (1984) reported a 10-fold increase in VIP concentration in the corpora cavernosa during pharmacologically induced erections. However, Kiely *et al.* (1987) found no such increase in VIP concentrations during similar studies on a larger group of subjects.

To assess the effect of exogenous VIP, Ottesen *et al.* (1984) injected 200 pmol VIP into the corpora cavernosa of 5 healthy men. The response was disappointing; only 1 man obtained an erection. In a double-blind, placebo-controlled trial of 24 impotent men it was found that VIP (in doses of 200 and 400 pmol) was not significantly associated with penile rigidity when compared with placebo (Roy *et al.*, 1988).

The smooth muscle relaxant papaverine and the alpha-adrenergic blocker phentolamine, given by intracavernosal injection, can both be used to induce a penile erection (Virag *et al.*, 1984; Blum *et al.*, 1985). A papaverine-phentolamine combination produced greater penile rigidity than papaverine alone (Zorgniotti and Lefleur, 1985; Sidi *et al.*, 1986). Junemann *et al.* (1986) found that intracavernosal papaverine in the dog resulted in a 300–700% increase in arterial inflow and a dramatic reduction in venous outflow. They also found that phentolamine produced a more modest (50–100%) increase in arterial inflow and had no effect on venous outflow. This group also reported that intracavernosal VIP resulted in a minor increase in arterial inflow, but caused active venous constriction and is important in maintaining an erection (Jünemann *et al.*, 1987).

There are no reported studies on the use of VIP in combination with other intracavernosal agents capable of inducing penile erections. This is a report on the erectile responses to different doses of VIP, alone and in combination with papaverine, phentolamine, and a papaverine–phentolamine combination.

Patients and Methods

Informed consent was obtained from 12 patients prior to inclusion in the study. Six men had

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predominantly psychogenic impotence, 2 had arteriogenic and 2 had neurogenic impotence; 1 patient with hypertension had been impotent since commencing atenolol and 1 was potent but had premature ejaculation. The mean age was 51 years (range 30–65). Pharmacologically induced penile erections were attempted with papaverine (pap), phentolamine (phen), a papaverine plus phentolamine combination (pap + phen) and vasoactive intestinal polypeptide (VIP) alone or in combination with other agents. The dosages are shown in Table 1.

The VIP was sterile and highly purified and was stored at −20°C in vials containing 4 μg VIP. The activity of the VIP was confirmed by performing radioimmunoassay as described by Long and Bryant (1982) on the contents of 10% of the vials from each batch.

All injections were performed under standard conditions on occasions at least 48 h apart.

In each of the 12 patients erections were induced with pap + phen, the standard combination of agents. The drugs used on the other occasions was decided by randomisation.

Those men who were to receive VIP had venous blood taken which was centrifuged for 10 min in a sterile container containing 100 units of heparin. The serum was collected in a sterile syringe and was used as a protein-containing medium for administration of the specified dose of VIP. Protein conjugation of the VIP prevented its adherence to the syringe and tubing.

All drugs were given with the patient supine using a 23 gauge butterfly needle inserted through the lateral aspect of a corpus cavernosum 2 cm proximal to the corona of the glans penis. The patient was then asked to stand and remain standing during a period of observation of at least 20 min. The penile rigidity response was graded by the same observer according to the Penrig scale (Table 2) (Virag *et al.*, 1984).

Table 1 Dosages of Drugs

Drug	*Dose*
Papaverine (pap)	90 mg
Phentolamine (phen)	2 mg
Papaverine plus Phentolamine (pap + phen)	30 mg 1 mg
Vasoactive intestinal polypeptide (VIP)	2 μg or 4 μg
Papaverine plus Vasoactive intestinal Polypeptide (pap + VIP)	30 mg 2 μg or 4 μg
Phentolamine plus Vasoactive intestinal Polypeptide (phen + VIP)	2 mg 2 μg or 4 μg
Papaverine plus Phentolamine plus Vasoactive intestinal Polypeptide (pap + phen + VIP)	30 mg 1 mg 2 μg or 4 μg

Table 2 Penrig (Penile Rigidity) Scale

< 10	No change in size of penis
10–30	Change in volume and size. No rigidity
30–50	Tumescence present
50–75	Tumescence is clear. Erection starts
75–100	Rigidity is achieved
> 100	Complete rigidity

Results

Table 3 shows the maximum Penrig scores (with delay in onset in minutes) following the various injected agents. A penile erection resulted in all subjects following intracavernosal pap + phen. On a separate occasion 9 of these men had VIP; 6 received 2 μg and 3 had 4 μg. The penile response with pap + phen was much greater in all 9 than with VIP alone, irrespective of the dose of VIP used. The penile rigidity response was graded by the same observer according to the Penrig scale (Table 2) (Virag *et al.*, 1984). This observer was unaware of the combination of drugs injected.

Three men (1 psychogenic, 1 neurogenic and 1 with arteriogenic impotence) had pap + phen + VIP. The Penrig score following this combination was greater by 20 points in 2 patients and 30 points in the other than with pap + phen.

Of the 4 patients (2 with psychogenic impotence, 1 with neurogenic impotence and 1 on antihypertensive medication) given pap + VIP, the Penrig response in 3 were comparable to those following pap + phen. The remaining patient on atenolol obtained a poorer response equal to that with pap alone.

Three men (2 with psychogenic and 1 with arteriogenic impotence) were given phen + VIP and pap + phen on different occasions. Each obtained a better erection with pap + phen. Two of these also had VIP alone and in both the Penrig responses with phen + VIP and VIP alone were similar. There were no complications in any patient. One patient with neurogenic impotence still had a fully rigid erection 3 h after a papaverine-phentolamine injections; however, detumescence began spontaneously at 4 h and was complete 1 h later.

Table 3 Maximum Penile Score following each Injection with its Delay in Onset (min)

Cause of impotence	*30 mg pap + 1 mg phen*	*2 µg VIP*	*4 µg VIP*	*30 mg pap + 1 mg phen + 2 µg VIP*	*60 mg pap*	*60 mg pap + 2 µg VIP*	*60 mg pap + 4 µg VIP*	*2 mg phen*	*2 mg phen + 2 µg VIP*	*2 mg phen + 4 µg VIP*
Psychogenic	75(10)	50(10)				70(10)				
Psychogenic	100(10)	10(5)								
Psychogenic	100(5)		40(10)		50(15)		90(5)			50(15)
Psychogenic	110(5)		60(5)		110(10)					
Psychogenic	90(10)							50(5)		60(5)
Psychogenic	80(10)			100(10)						
Premature ejaculation	110(5)	70(20)								
Neurogenic	100(5)	80(10)			80(10)	90(10)				
Neurogenic	60(10)		50(10)	90(15)						
Arteriogenic	100(5)	60(10)							50(10)	
Arteriogenic	70(10)			90(5)						
Hypertension	75(10)	20(10)			50(5)		50(5)			

Discussion

This study, using exogenous VIP by intracavernous injection, confirms the previous experience of Ottesen *et al.* (1984) that VIP is poor at inducing human penile erections. The dose of VIP used by Ottensen was 0.6 µg but in this study much greater doses of VIP (2 and 4 µg) were employed without any significant benefit.

This study demonstrates that VIP can potentiate the erectile response to intracavernosal papaverine or a papaverine-phentolamine combination.

The studies by Jünemann *et al.* (1986, 1987) may help to explain this effect. They found that papaverine had a major and VIP a minor effect on increasing penile arterial flow. However, both of these agents had a potent effect on increasing venous outflow restriction. Using immunohistochemical studies on penile tissue in the flaccid and erect states, they showed that the distribution of VIP increased in the area between the cavernosal smooth muscle and sinusoidal spaces during the erection phase. Increased filling of the sinusoids probably increases intracorporeal pressure, causing occlusion of the subalbugineal venular plexus and reduced venous return.

The poor erectile response using intracavernosal VIP alone suggests the existence of another (or several) neurotransmitters with a potent vasodilator effect on arterial inflow. It is also tempting to speculate that the reduced concentration of VIP in the penises of impotent men found by Polak *et al.* (1981) results in a reduced capacity to diminish venous return *in vivo*. This peptide may modulate or potentiate the effect of this as yet unknown arterial vasodilator. In a similar manner the response to papaverine may be potentiated by the combined use of VIP.

The inability of the phentolamine—VIP combination to induce erections can be explained by the limited ability of each of these agents to increase arterial flow. Difficulties in the production and stability of VIP make its use in combination with currently used vasoactive agents impractical at present in the management of erectile impotence. However, further studies using exogenous VIP in combination with other vasoactive agents, perhaps employing VIP antibody, may help to explain the exact mode of action of these agents. This study provides further evidence for the veno-occlusive effect of VIP.

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Case Reports

Technique for Relieving Vascular Obstruction of the Superior Infundibulum (Fraley's Syndrome)

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Case Report

A 24-year-old woman with a history of persistent right costovertebral ankle pain was admitted with right flank pain and macrohaematuria. An IVU showed a non-obstructing stone below the right pelviureteric junction, with mild pyelectasis and middle/inferior caliectasis. Marked dilatation and clubbing of the superior calix were also present, with delayed emptying and a persistent filling defect in the infundibulum. No relation could be found between the stone and the upper caliectasis

Exploration was carried out to remove the stone and to relieve a probable vascular obstruction of the upper infundibulum. Pyelotomy was performed through a twelfth rib incision and the stone removed. The branches of the renal vessels were exposed by dissection in the pyelorenal sinus. The artery to the posterior vascular segment was obstructing the superior infundibulum by compressing it against the overlying renal substance, after entering the renal sinus. An intrinsic obstruction of the infundibulum was excluded and Fraley's syndrome was diagnosed (Fraley, 1966). The obstructing artery was carefully mobilised to obtain a vessel as straight as possible. The artery was elevated and dorsally invaginated within a tunnel formed from the renal tonaca fibrosa by cutting and re-suturing a flap to its bed (Fig. 1A). Fixed in this position, the artery remained away from the infundibulum and the obstruction was relieved (Fig. 1B).

The post-operative course was uneventful. There was a gradual improvement in flank pain and the patient was asymptomatic 17 months post-operatively. The urogram 3 months after operation showed no upper caliectasis and no filling defect in the infundibulum.

Comment

Unlike other techniques used to correct the vascular abnormality in Fraley's syndrome, the operative procedure performed in our patient seems free from complications.

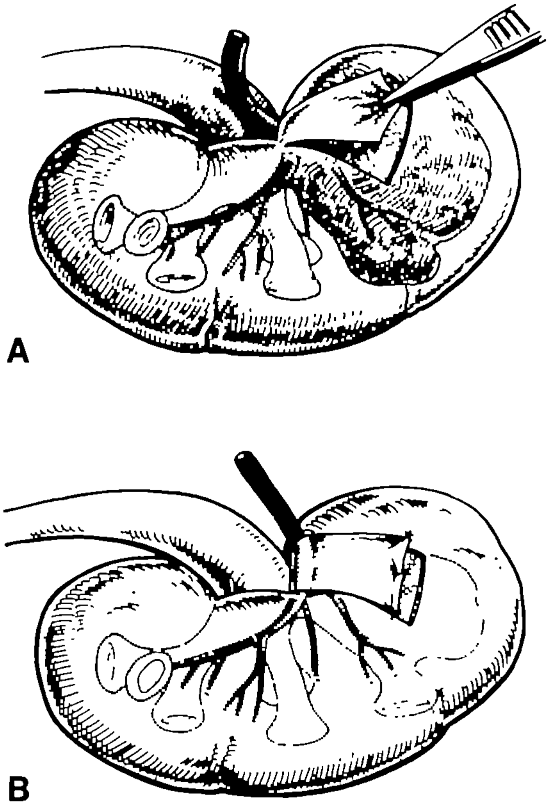

Fig.

Reference

Fraley, E. E. (1966). Vascular obstruction of superior infundibulum causing nephralgia: a new syndrome. *N. Engl. J. Med*, **275**, 1403–1409

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Stalactites and Stalagmites: Crystal Formation on Ureteric Double-J Stents

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Case Reports

Case 1. A 38-year-old man, who had undergone a left nephrectomy for pyonephrosis and calculus 3 years previously, presented with a 36-h history of anuria. Serum creatinine, which had previously been normal, was 0.37 mmol/l (normal 0.05–0.12 mmol/l). A double-J stent was inserted under local anaesthesia and renal function returned. In view of his history of uric acid calculi, urinary alkalinisation was commenced and continued for a period of 6 weeks, following which the stent was removed. Figure 1 shows the renal end of the ureteric stent with a "cap" of crystallisation which extended along the distal cm and which contained urate and oxalate.

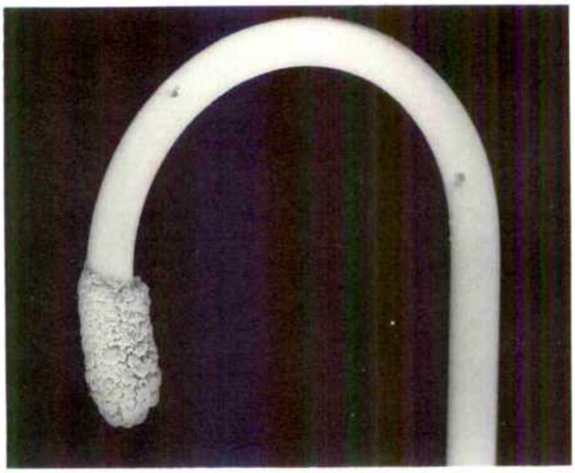

Fig. 1 Urate and oxalate crystal formation on the renal end of a double-J stent.

Case 2. A 61-year-old woman with no history of urinary tract calculi underwent a pyeloplasty for pelviureteric junction stenosis. A ureteric double-J stent was inserted at the time of the procedure and removed 6 weeks post-operatively. Inspection of the stent revealed that the majority of the side holes were plugged with crystals and an encircling crystallisation (Fig. 2) was seen 7 cm from the vesical end. Analysis of the crystallisation revealed calcium, ammonium, phosphate and oxalate.

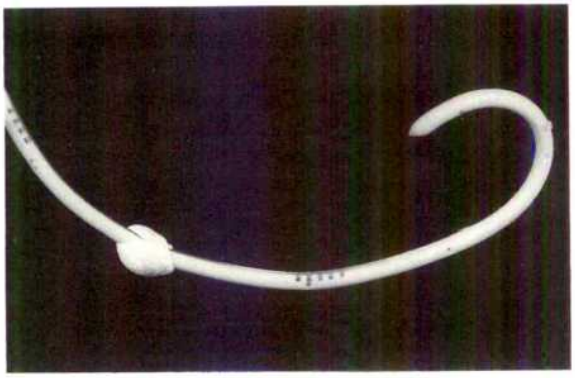

Fig. 2 Calcium, ammonium, phosphate and calcium oxalate crystals enveloping the lower end of a double-J stent. A side hole on the apex of the "J" is plugged with the same substance.

Case 3. A 41-year-old man underwent extracorporeal shock wave lithotripsy for a 2.5-cm renal pelvic calculus; a double-J stent had been inserted before the procedure. When he attended for cystoscopic removal of the stent, cystoscopy revealed crystallisation along a 3-cm segment of the vesical end of the stent. It was not possible to remove the stent until the crystallisation had been removed and in order to do this it was necessary to use the Storz Mauer-Mayer stone punch. The double-J stent was then extracted and the stone fragments removed from the bladder. Analysis revealed the crystallisation to contain calcium, magnesium, ammonium and phosphate.

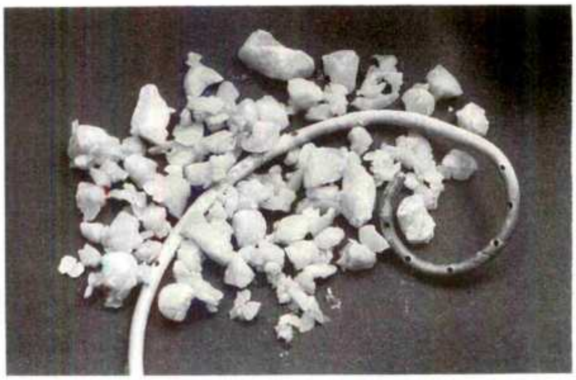

Fig. 3 Calcium, magnesium, ammonium and phosphate crystals at the vesical end of a double-J stent from which they had to be broken to enable removal of the stent.

Comment

Complications of ureteric stents include dysuria and urgency, which frequently respond to treatment with anti-spasmodic drugs. Vesicoureteric reflux, flank pain and discomfort may also be experienced. Migration of the stent may occur and more serious complications include bacteriuria, pyelonephritis and sepsis secondary to encrustation of the stent and stone formation. Most stent obstructions occur within 2 months of placement (Shore *et al.*, 1987). Pocock *et al.* (1986) advised replacement of the stent every 6 weeks for stone formers. Kearney *et al.* (1979) suggested that ureteric stents should be replaced every 6 months in order to prevent encrustation and obstruction. Pocock *et al.* (1986) also recommended regular X-rays and checks of renal function. Spirnak and Resnick (1985) reported stone formation at the proximal and distal ends of the catheter as early as 3 weeks after placement in patients with a history of urolithiasis. In the 3 patients reported here, all stents were removed in less than 2 months, but calcification had occurred in each case.

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Pararenal Pseudocyst Secondary to Bladder Tumour

J. P. MacDERMOTT and B. K. GRAY, *Department of Urology, Royal Infirmary, Bradford*

Case Report

A 58-year-old male patient was referred complaining of right upper abdominal and loin pain for 5 weeks. He admitted to slight urinary frequency, dysuria and haematuria on one occasion only.

Examination revealed a right upper abdominal mass. An ultrasound scan showed a large cystic mass behind the right kidney extending down along the psoas muscle and hydronephrosis of the kidney. A CT scan confirmed this (Fig. 1) and showed the right ureter to be dilated down to the bladder. The bladder wall was thickened at the vesicoureteric junction and this area showed vascular enhancement following the injection of contrast (Fig. 2), suggesting a bladder neoplasm. A tumour was subsequently resected from the area of the right ureteric orifice and proved to be a moderately differentiated transitional cell carcinoma with invasion of muscle.

Before referring the patient for radiotherapy, needle aspiration of the pararenal cyst was performed. This yielded 500 ml of sterile fluid.

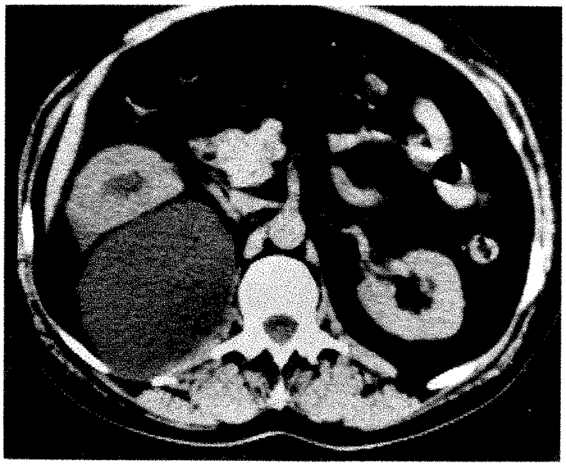

Fig. 1

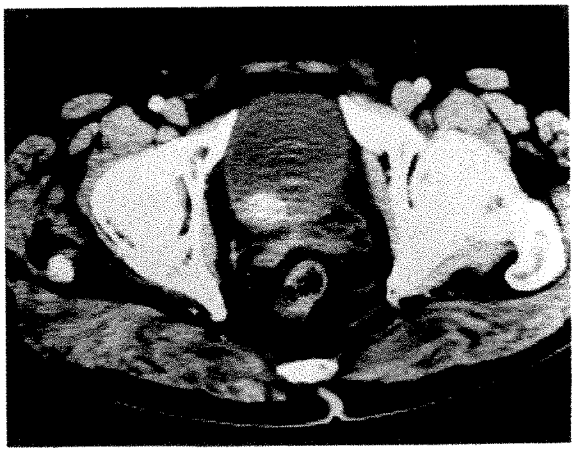

Fig. 2

Comment

Pararenal pseudocyst is a recognised complication of nephroureteric trauma and of surgery on the renal pelvis and upper ureter. It has also been reported following lower abdominal surgery (Worrell, 1985) and lower ureteric calculus obstruction (Leemans and Kotowicz, 1977). Ureteric obstruction due to bladder tumour occurs gradually and does not usually lead to the high intraureteric pressure which would cause extravasation. In this case, a large extravasation of urine followed ureteric obstruction from a bladder tumour at the ureteric orifice.

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Unusual Metastasis of Bladder Cancer

A. REBELAKOS, A. MANTHOPOULOS and G. G. HADJISSOTIRIOU, *Department of Surgery/Urology, Greek Anticancer Institute and Hygeia Diagnostic and Therapeutic Center, Athens, Greece*

The usual sites of bladder cancer metastases are lymph nodes, liver, lungs and bone (Fetter *et al.*, 1959). We report 2 cases of uncommon metastases to the skin.

Case Report

Two patients with bladder cancer who eventually developed malignant skin lesions were admitted over a 2-year period. Both tumours were classified as G3 and at least T3a transitional cell carcinoma after intravenous urography, cytology, examination under anaesthesia and biopsy. Both were treated with radical radiotherapy. Two months after treatment the first patient was readmitted with a painful skin nodule at the left mid-sternum. This was excised and biopsy showed transitional cell carcinoma (G3) on healthy tissue; 4 weeks later the patient was readmitted with a local recurrence (Fig.). Local radiotherapy was ineffective and the patient died within a month. The second patient, who had a similar problem, was treated with local radiotherapy without excision. The skin nodule was not palpable 6 months after treatment.

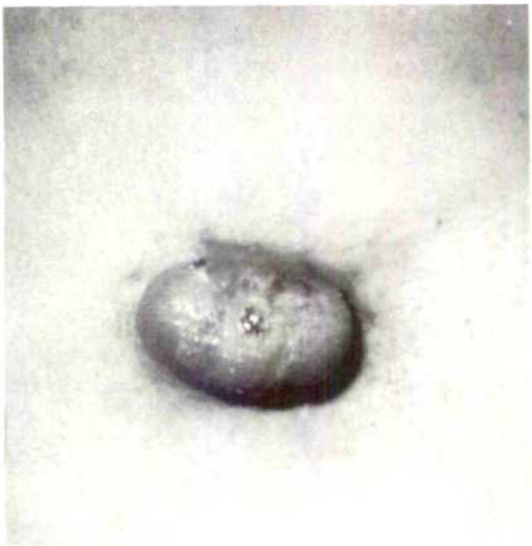

Fig.

Comment

Except for the sites stated, other distant metastases of bladder cancer appear to be rare (Webb, 1985). Kishi *et al.* (1981) reported that all patients with T3 and T4 tumours had metastatic disease, and the most uncommon sites appeared to be skin, kidney, pancreas and myocardium. The cases described here may indicate that radiotherapy without excision might be the recommended palliative treatment.

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Requests for reprints to: G. G. Hadjissotiriou, Department of Surgery/Urology, Hygeia Hospital, Kifissias and Er. Stavrou 4, Maroussi, Athens, Greece.

Catheters: a Knotty Problem!

D. J. JONES and T. A. McNICHOLAS, *St Peter's Hospital, London*

The use of narrow nasogastric tubes to splint narrow urethral strictures when Foley catheters cannot be introduced is a well tried technique. This report demonstrates an unusual complication.

Case Report

A 51-year-old man had sustained a rupture of the penile urethra 3 years previously and had been treated elsewhere by suprapubic catheterisation and subsequent optical urethrotomy. He presented to us with outflow obstruction and a 2 × 2 cm hard mass on the ventral mid-shaft of the penis where a urethrogram showed a tight stricture. A limited urethrotomy was performed with difficulty. It was not possible to pass a Foley catheter and a 10 gauge feeding tube was therefore passed into the bladder through the sheath of a small cystoscope and attached to the penis with adhesive tape.

Attempts to remove the catheter at 48 h were at first unsuccessful, but eventually it was withdrawn with the

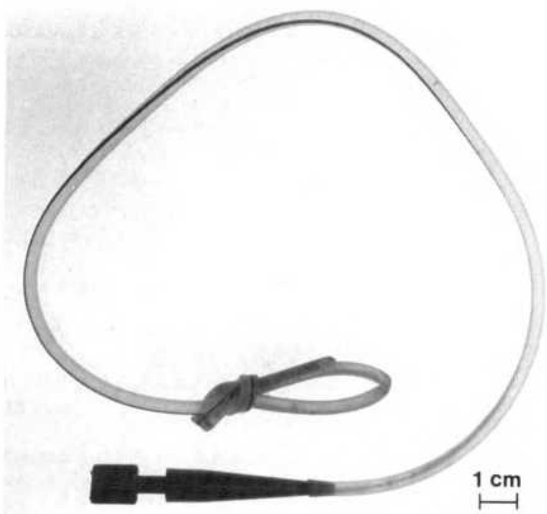

Fig. 1 Knotted nasogastric tube after removal from urethra.

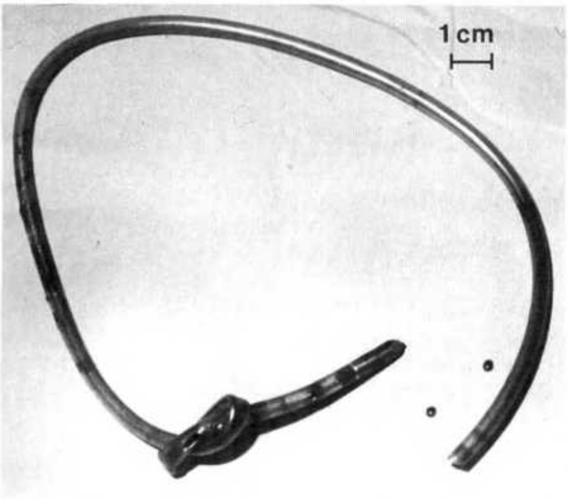

Fig. 2 Knotted nasogastric tube after removal from stomach.

aid of lignocaine lubricant and steady traction. To the surprise of both patient and surgeon the catheter was found to be knotted (Fig. 1). Afterwards the patient voided normally and is awaiting urethroplasty.

Comment

Plastic feeding tubes are cheap, easily available and are useful for splinting and draining the bladder when Foley catheters cannot be introduced. They are, however, very long and should be shortened to avoid leaving an excessive length in the bladder which may subsequently knot. A similar knot has been seen in a long nasogastric tube used to splint an oesophago-gastric anastomosis (Fig. 2).

Requests for reprints to: Wing Commander D. J. Jones, The Princess of Wales Royal Air Force Hospital, Ely CB6 1DN.

Tension Pneumoperitoneum: an Unusual Urological Cause

A. YIP, W. Y. LAU and K. K. WONG, *Government Surgical Unit, Queen Mary Hospital, Hong Kong*

Tension pneumoperitoneum is a rare but well recognised clinical entity. We report an unusual case of carcinoma of bladder complicated by tension pneumoperitoneum with accompanying respiratory embarrassment. There is no previous report of a urological cause for tension pneumoperitoneum.

Case Report

A 75-year-old woman presented with painless wholestream haematuria and clot retention. Emergency cystoscopy revealed a bleeding tumour 3 cm in diameter with a necrotic centre. Clot evacuation and biopsies were performed. Continuous bladder irrigation was instituted via a 20F 3-way Foley catheter. Biopsies showed transitional cell carcinoma (grade II).

Two days later, shortly after the bladder irrigation was stopped, the patient suddenly complained of severe abdominal distension and dyspnoea. On examination, the abdomen was tensely distended with no tenderness or rigidity. The percussion note was tympanitic over the abdomen and the loins. Subcutaneous emphysema was noted over the left loin. The spigot of the irrigation channel of the Foley catheter was found to be loosened. Chest X-ray and KUB showed a large amount of free gas under the diaphragm with no dilated bowel shadow (Fig.). She deteriorated rapidly and became cyanotic. Immediate laparotomy was performed. On entering the peritoneal cavity, a gush of odourless gas escaped under great pressure and the anterior abdominal wall collapsed. There was no peritoneal soiling. No perforation could be demonstrated throughout the whole gastrointestinal tract. A large amount of gas bubbles was found in the retroperitoneum of the left pelvis adjacent to a tumour of the urinary bladder with full thickness involvement. There was no obvious perforation. Bladder irrigation was resumed during operation and there was no fluid leakage. A tubal drain was placed in the pelvis and the abdomen closed. The post-operative course was uneventful.

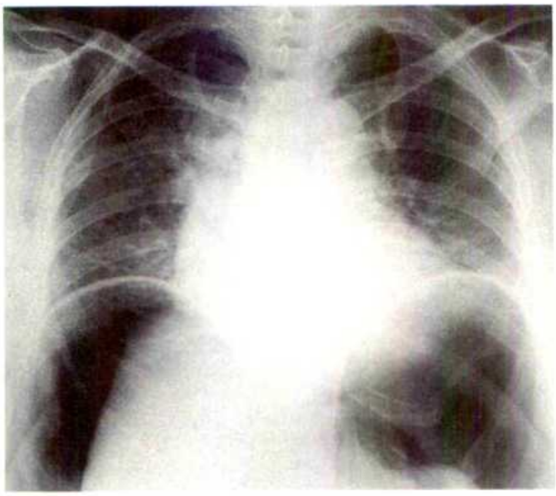

Fig. Chest radiograph showing large amount of free gas under the diaphragm.

Comment

Tension pneumoperitoneum arises exclusively from the excessive quantity of air or gas trapped under pressure in the abdominal cavity. It is characterised by the presence of a valve-like mechanism similar to that found in tension pneumothorax (Lagundoye and Itayemi, 1970). This valve-like mechanism prevents the free extravasation of fluid into the peritoneal cavity but permits the escape of air with a resultant increasing abdominal distension without peritonitis or ileus (Meyers *et al*., 1935).

In our patient, with the negative intra-abdominal pressure generated during each respiratory cycle, air was sucked into the bladder through the irrigation channel of the Foley catheter. With a high intravesical pressure maintained by the negative intra-abdominal pressure and a valve-like mechanism in the necrotic tumour bed of the bladder which allowed only air to escape but not fluid, tension pneumoperitoneum was generated. It has been reported that the site of perforation for tension pneumoperitoneum might not be found at operation or autopsy (Lagundoye and Itayemi, 1970). Pneumoperitoneum, but not tension pneumoperitoneum, has been described after cystoscopy and the site of leakage could not be demonstrated even on cystography immediately following the event (Zer *et al*., 1978).

The early recognition of tension pneumoperitoneum is of utmost importance since it may cause life-threatening respiratory insufficiency, as in our case. We advocate urgent abdominal paracentesis for decompression of the peritoneal cavity prior to exploratory laparotomy.

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Requests for reprints to: A. Yip, Department of Surgery, Kwong Wah Hospital, Kowloon, Hong Kong.

Squamous Intra-epithelial Neoplasia Presenting as a Urethral Caruncle

D. NEILSON, J. B. F. GRANT and C. E. T. SMITH,
Departments of Urology and Pathology, Northern General Hospital, Sheffield

Case Report

A 31-year-old female presented with a 4-month history of a swelling at the urethral orifice. The lesion was painful on intercourse and she had post-coital and intermenstrual bleeding. Examination revealed a urethral caruncle 1.5 cm in diameter which was excised. Histological examination showed a polypoid lesion composed of squamous epithelium with changes of grade 3 intra-epithelial neoplasia and areas compatible with infection by human papillomavirus (HPV) on an oedematous, inflamed stroma (Figs 1 and 2). There was no history of genital warts and several cervical smears over the previous 13 years had all been normal.

Colposcopy was performed and a suspicious area around the cervical os was biopsied. Cervical intra-epithelial neoplasia grade 3 (CIN-III) was present and subsequent cone biopsy was performed; no evidence of invasion was found and excision was complete.

Comment

Urethral caruncles are commoner in post-menopausal women but do not appear to represent a single clinical entity. Marshall *et al*. (1960) reported a variety of benign and malignant tumours that presented in this way. It is important therefore, especially in the younger women, that all cases are excised, or at least biopsied, and examined histologically. As our case demonstrates, should squamous intra-epithelial neoplasia be found, then examina-

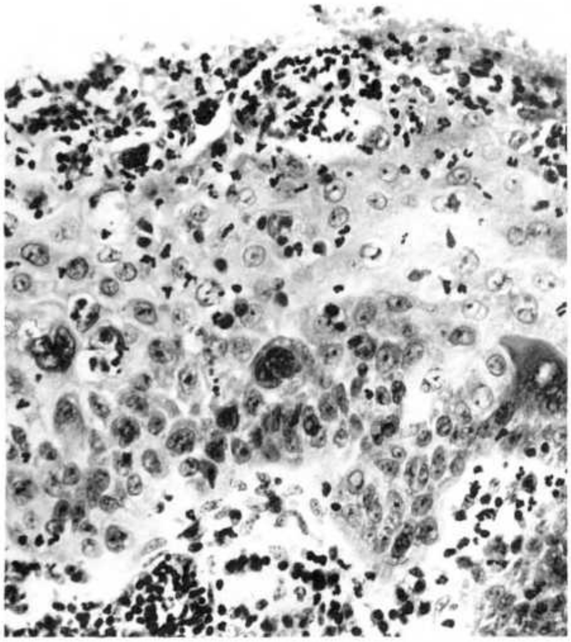

Fig. 1 Inflamed squamous epithelium containing bizarre multinucleate cells suggestive of HPV infection. Typical koilocytes are not seen. (H and E × 250).

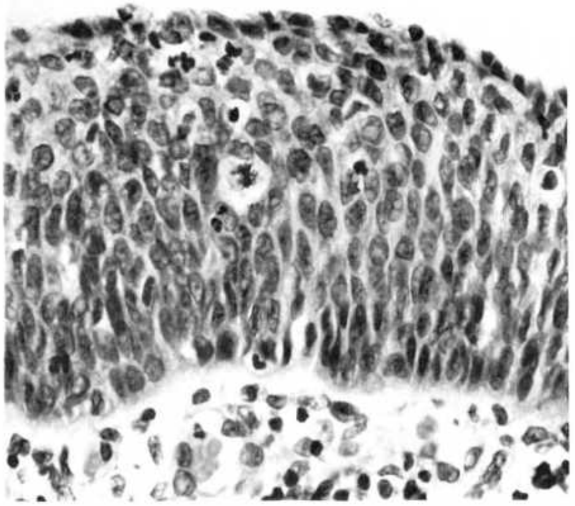

Fig. 2 CIN-III squamous epithelium showing complete loss of cellular maturation, reversal of nuclear polarity and displaced, abnormal mitotic figures. (H and E × 330).

tion of the rest of the lower genital tract is necessary to exclude further lesions.

This case also illustrates changes of HPV infection in the region of intra-epithelial neoplasia. Although the precise association between these two is still speculative, HPV DNA has clearly been shown in both CIN and early vulval neoplasia (Gupta *et al.*, 1987).

Acknowledgement

The authors thank Dr J. H. F. Smith for his comments on this case.

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Association between Squamous Cell Carcinoma of the Renal Pelvis and Calculi

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Department of Urology, Hédi Chaker Hospital, Sfax, Tunisia

Case Reports

Case 1. T.K., a 57-year-old man, was admitted with a 3-month history of left loin pain. Physical examination and blood chemistry were normal. Urine culture grew *Proteus mirabilis*. IVU revealed a left staghorn calculus within a horseshoe kidney. At operation an infiltrating tumour of both the upper pole of the left kidney and adrenal gland was discovered. Microscopic examination showed a keratinising squamous cell carcinoma (Fig.) arising from the renal pelvis and upper calix. The patient's condition deteriorated and he died 7 months later.

Case 2. B.T., a 52-year-old woman, was admitted with left lumbar pain associated with chills and fever. A tender abdominal mass was present. Ultrasound and IVU revealed renal destruction and a lower pole calculus. The nephrectomy specimen showed multiple papillary growths in a lower pole distended calix. Microscopy showed a squamous cell carcinoma associated with a transitional cell carcinoma containing foci of squamous metaplasia. The patient's condition worsened rapidly and she died within 2 months of operation.

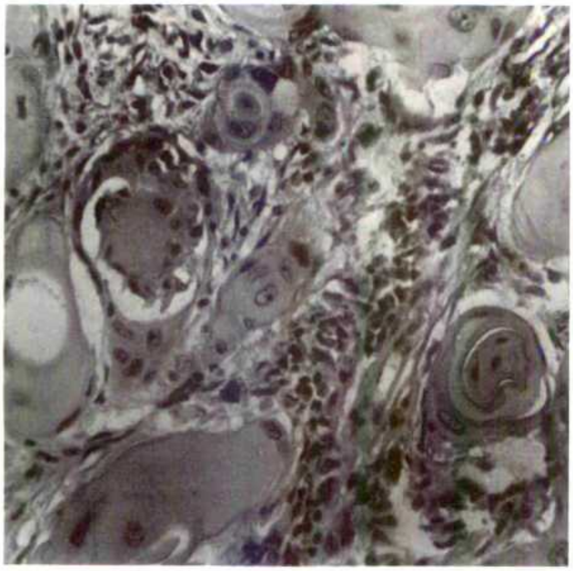

Fig. Nests of squamous cell carcinoma with keratin pearls. (H and E × 72. Enlargement × 4.66).

Case 3. G.J., a 47-year-old man, was admitted with right loin pain. He had undergone right pyelolithotomy 6 years previously. IVU showed a non-functioning right kidney. The nephrectomy specimen contained an infiltrating and well differentiated squamous cell carcinoma arising from and completely obstructing the renal pelvis. The patient's general condition deteriorated and he died 8 months later.

Comment

Tumours of the renal pelvis and calices represent 5 to 14% of all malignant renal growths and less than 1% of genitourinary tumours (Latham and Kay, 1974; Li and Cheung, 1987). Squamous cell carcinoma is estimated to represent 9 to 20% of tumours of the renal pelvis and to be associated with calculi in 30 to 60% of cases (Mazeman, 1972). The 3 cases reported here illustrate this association. Urinary calculi are accepted as a main carcinogenic risk factor for squamous cell carcinoma. Chronic irritation and infection are believed to induce reactive changes in the urothelium and lead via metaplasia and leukoplakia to neoplasia. Staghorn stones are more likely to be associated with renal pelvis neoplasms but smaller calculi within a hydronephrosis or a pyonephrosis could be associated with such growths. Some authors believe that, in cases where no stones were found, the tumour might have been initiated by previous calculi which were either passed or removed (Latham and Kay, 1974).

Pre-operative recognition of such tumours is difficult since most of the symptoms are obscured by the presence of the stone and most imaging aids are unhelpful (Li and Cheung, 1987). Treatment should entail nephrectomy and only partial ureterectomy as renal squamous cell carcinomas, unlike transitional cell tumours, have no propensity to spread downwards. Chemotherapy conveys little benefit and the value of radiotherapy is debatable. The prognosis remains generally very poor despite reports of 5-year survival (Latham and Kay, 1974; Li and Cheung, 1987).

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British Journal of Urology (1989), **64**, 203–204

0007-1331/89/0064-0203/$10.00

Points of Technique

Renal Denervation with Releasing Renal Capsule Incision in the Loin Pain/Haematuria Syndrome

A. R. E. BLACKLOCK, *Department of Urology, Walsgrave Hospital, Coventry*

The loin pain/haematuria syndrome is an uncommon condition which predominantly affects young women. It was first described by Little *et al.* (1967). The symptoms consist of recurrent loin pain and tenderness, which may be severe and continuous, associated with haematuria, either frank or microscopic. The diagnosis is established by renal angiography and renal biopsy (Aber and Higgins, 1982).

The underlying disease is not treatable by medical or surgical means. However, renal denervation with releasing renal capsule incision will relieve the pain.

The renal nerve supply is entirely autonomic, comprising sympathetic, efferent and afferent fibres with a minor contribution of parasympathetic fibres from the vagus. The autonomic nerve fibres travel into and from the kidney in close association with the arterial blood vessels, starting with the renal artery.

There are 2 possible explanations for renal pain. Firstly, chronic stretching of the renal capsule due to swelling of the underlying renal parenchyma, related to the vascular abnormalities of the syndrome, could stimulate afferent nerve endings in the capsule. Alternatively, swelling of the renal parenchyma within the non-elastic renal capsule could stimulate afferent nerve endings around the intralobular arteries by the increased pressure. The swelling of the renal parenchyma need not be very great to cause pain from the capsule or intralobular nerve endings.

Fully incising the renal capsule will release tension in the capsule and parenchyma and so relieve the pain.

Technique

A young female patient with increasingly incapacitating left loin pain due to the loin pain/haematuria syndrome underwent the following procedure.

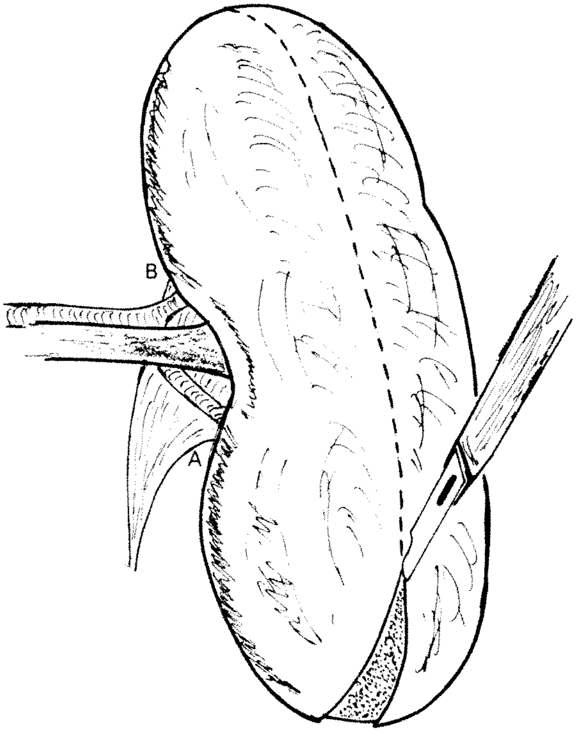

Fig. All tissue stripped from vessels entering or leaving renal hilum and upper ureter—to denervate kidney. Renal capsular incision completely around longitudinal peripheral border from A to B.

The left kidney was exposed and mobilised via a standard loin incision. Perinephric fat was freed, following which all adventia, fibrous tissue, nervous tissue and lymphatic tissue were stripped off the divisions of the renal artery and vein, proceeding proximally towards the aorta and the IVC as far as was technically feasible and safe. The upper end of the ureter was similarly cleared. The renal capsule was then incised through its full thickness along the complete longitudinal peripheral border (Fig.) At the end of this procedure the incised edges of the capsule were some 0.5 cm apart. The loin incision was closed in the standard way.

The patient made an uneventful recovery from the operation. Renal function was unchanged and the patient remains pain-free 18 months postoperatively.

Comment

Previous treatments to relieve the pain in the loin pain/haematuria syndrome have attempted only to denervate the kidney. Chemical means include phenol sympathectomy and splanchnic nerve blockade. Surgical means include surgical sympathectomy and, more recently, renal autotransplantation. Such treatments fail eventually because of regeneration of autonomic nerves. Autotransplantation was thought to overcome this problem. However, Hutchison *et al.* (1987) reported a case of apparent re-innervation of a kidney autotransplanted for severe loin pain/haematuria syndrome 12 months after operation.

It is probable that in the technique described, capsule incision alone will cure the renal pain and denervation may be an unnecessary addition. More patients will be needed to determine this. Complete capsulectomy is considered unnecessary and, indeed, the resulting extensive scar tissue might negate the decompression effect of the capsulectomy.

The technique of renal denervation with releasing renal capsule incision, as described, has no renal morbidity and is a satisfactory surgical treatment of renal pain in the loin pain/haematuria syndrome.

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The Control of Incontinence in Spina Bifida

G. C. WISHART, W. A. S. TAYLOR and G. ORR, *Department of General Surgery, Inverclyde Royal Hospital, Greenock*

We report an alternative method of treatment of incontinence in 2 spina bifida patients.

Patient 1. A 24-year-old man with spina bifida presented in September 1987 with incontinence and a urethral stricture following a 6-year history of urethral catheterisation. An IVU and routine tests of renal function were normal. His urethral stricture required urethrotomy on 2 occasions but following removal of his catheter his incontinence persisted.

Patient 2. A 21-year-old man with spina bifida presented in March 1987 with dribbling incontinence and excoriated penile skin secondary to penile sheaths worn since 1979. Prior to this an indwelling catheter was removed following bladder calculus formation. His renal function was normal. Following circumcision to excise a large redundant foreskin, it became impossible to attach an external collecting system due to penile atrophy.

Technique

The skin around the base of the penis was shaved and cleaned. A flange was passed over the penis and applied. A Surgicare System 2™ Combihesive Urostomy Pouch (Squibb Surgicare Ltd, Hounslow) with an Accuseal™ Tap was attached to the flange. The Accusal Tap was connected to a standard drainage bag. The flange was replaced every few days.

Comment

Incontinence develops in 95% of patients with untreated myelomeningocele (Walsh *et al.*, 1986). The main aims of treatment are to preserve renal function and attain continence.

The use of conventional collecting systems or urethral catheterisation is not without complication. Surgical intervention is not always appropriate or successful.

In our patients this system provided a comfortable means of external collection which did not leak. Both still require regular shaving to maintain strong adhesion but neither has had trouble with skin excoriation or ulceration to date.

Both patients are now totally dry and 1 returned home after many years in an institution.

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0007-1331/89/0064-0205/$10.00

Correspondence

Dear Sir,
re **Calcification in a renal oncocytoma.** A. R. Cato. *Br. J. Urol.*, **62**, 486–487, 1988.

In the above article the author describes a case of oncocytoma with calcification. He comments that this is the first case reported in the literature. We recently had the opportunity of studying a similar case and a search of the literature revealed that N. F. Wasserman and S. L. Ewing (*A. J. R.*, **141**, 747–749, 1983) described the first case of calcification in an oncocytoma. B. M. Giuffre and D. J. Gulliver (*Australas. Radiol.*, **28**, 120–123, 1984) also detected the presence of calcium in an oncocytoma.

Yours sincerely,

J. R. Varela and F. G. Veiga
Avda de Monelos 19–23, 3°D, 15008 La Coruña, Spain.

Dear Sir,
re **The value of cystourethroscopy in the investigation of microscopic haematuria in adult males over 40 years. A prospective study of 100 patients.** D. J. Jones *et al. Br. J. Urol.*, **62**, 541–545, 1988.

I am pleased that Mr R. W. Lloyd-Davies found the above article of value and I read the anecdotal case report in his letter (*Br. J. Urol.*, **63**, 446, 1989) with interest. He appears, however, to have missed the point of our study which clearly shows that a *careful* history and examination with (in his patient) examination of the urine for ova will result in a diagnosis in almost all cases. Obviously if simple investigations suggest further pathology, then a cystoscopy may be necessary.

With increasing worldwide travel, especially to exotic locations, the importance of obtaining a history of possible exposure to tropical diseases cannot be stressed too greatly.

Yours sincerely,

D. J. Jones
Princess of Wales Royal Air Force Hospital, Ely, Cambridgeshire CB6 1DN.

Dear Sir,
re **Prazosin-induced priapism.** N. Bullock. *Br. J. Urol.*, **62**, 487–488, 1988.

We have read with interest the above article and feel that drug-induced priapism may be more frequent than previously suspected. Many cases of idiopathic priapism could be associated with the use of drugs (Winter, C.C. *J. Urol.*, **125**, 212, 1981) and S. Adjiman *et al.* (*Ann Urol.*, **22**, 125–128, 1988) showed this aetiology in more than 50% of a series of 31 patients with priapism. The incidence of drug-induced priapism is probably increasing as a result of the widespread use of intracorporeal injections of vasoactive agents to induce penile erection in impotent patients. R. E. Nellans *et al.* (*J. Urol.*, **138**, 52–54, 1987) reported that these procedures can produce priapism in 8.7% of patients.

Antihypertensives have often been associated with priapism. In his article Bullock quoted some cases of priapism with guanethidine, hydralazine and prazosin. However, phenoxybenzamine and labetalol can also produce priapism, although the link is not as clear as with prazosin (J. E. Baños *et al. Med. Toxicol.*, **4**, 46–58, 1989). We disagree with the statement that only 3 cases of priapism associated with prazosin have been reported: 9 additional case reports have been published since the first report in 1979 (J. E. Baños *et al. Med. Toxicol.*, **4**, 46–58, 1989). More recently another patient with prazosin-induced priapism was reported by S. Siegel *et al.* (*Br. J. Urol.*, **61**, 165, 1988).

The reversal of priapism with metaraminol is an interesting finding. Its usefulness has been shown in treating priapism secondary to leukaemia (A. Stanners and D. Colin-Jones. *Lancet*, **2**, 978, 1984), promazine (J. Kogeorgos and C. De Alwis. *Br. J. Psychiatry*, **149**, 241–243, 1986) and following the intracorporeal injection of vasoactive drugs for impotence. If metaraminol can reverse the priapism secondary to drugs such as prazosin, antipsychotics or trazodone, it will form an interesting alternative to surgical treatment in some patients with drug-induced priapism.

Yours sincerely,

J. E. Baños and F. Bosch
Departament de Farmacologia i Psiquiatria, Universitat Autonoma de Barcelona, 08193 Bellaterra (Barcelona), Spain.

Reply by N. Bullock. I am grateful to Drs Baños and Bosch for drawing my attention to further evidence on prazosin-induced priapism, some of which was published after submission of my original manuscript. It is important to differentiate between cases where prazosin was responsible in overdose, either self-inflicted or as a result of associated disease, and cases where prazosin was implicated when used in normal therapeutic doses. Similarly, in some reports, factors other than prazosin alone can be implicated in the development of priapism.

I agree that drug-induced priapism is probably more common than has previously been thought. In patients with "idiopathic" priapism, drug consumption should always be investigated and I would suggest that treatment with intracorporeal metaraminol should be tried before resorting to surgical shunting. This needs to be used with extreme caution, however, in hypertensive patients if their drug therapy is thought to be responsible for their priapism.

British Journal of Urology (1989), 64, 207–208

Notices

British Association of Urological Surgeons

President: R. T. Turner-Warwick, DSc, DM, MCh, FRCP, FRCS, FACS

Annual Meeting. Scarborough. 10–13 July 1990

Abstracts of contributions to be considered as either papers, posters or videos by the Programme Sub-Committee of Council should be submitted on the special forms available from the BAUS Secretariat. Completed forms, which should state clearly whether the submission is a paper, a poster or a video, must be returned to the Honorary Secretary by Friday, 5 January 1990.

Abstracts not on the special forms will NOT be considered.

All correspondence to: M. G. Royle, FRCS, Honorary Secretary, British Association of Urological Surgeons, Royal College of Surgeons, Lincoln's Inn Fields, London WC2A 3PN.

British Association of Urological Surgeons

President: R. T. Turner-Warwick, DSc, DM, MCh, FRCP, FRCS, FACS

Autumn Meeting: Churchill College, Cambridge. 29 and 30 September 1989

The Day Meeting of the Association on 30 September will be preceded by a Postgraduate Teaching Afternoon on 29 September, when the topic will be "Pre- and Post-natal Diagnosis and Management of Urinary Anomalies".

Further information from: R. H. Whitaker, Department of Urology, Addenbrooke's Hospital, Hills Road, Cambridge CB2 2QQ.

C.-E. Alken Prize

An endowment fund has been established to further clinical work and research in the field of Urology by presenting an annual award of SwF 10,000 for outstanding scientific endeavours. The award will be for an unpublished work in the field of Urology. An award certificate will also be presented. The prize money may be divided among several contributors.

The papers may be written in either German or English and three copies must be submitted by 30 September 1989 to: Stiftungsrat C.-E. Alken-Stiftung, Advokaturbüro Dr F. Kellerhals, Bundesplatz 4, CH-3011 Bern, Switzerland.

Each submission must be affixed with a code word and must not bear the author's name. In addition, a sealed envelope labelled with the code word is to be included, containing on a separate sheet of paper the author's name and professional standing, together with the code word.

The adjudicators for the award will be the Board of Directors of the endowment fund and their decision will be final.

The Surgitek Prize

The Prize consists of a fully sponsored visit to the American Urological Association Annual Five-day Meeting, together with a tour of Surgitek's manufacturing facility in Racine, Wisconsin. It is open to trainees in urology and consultants who are within 5 years of first appointment. Entrants should submit a written paper, which may be on any subject, but must be unpublished, and must not have been submitted previously for the Surgitek Prize, or other prizes. The winning entry will be the one which is considered to be "The most significant contribution to urology".

Entries will be judged by three members of BAUS Council nominated at the October meeting of Council. Papers should be submitted in triplicate to the Honorary Secretary by 1 January each year.

Hans Marberger Prize

The Hans Marberger Prize will be awarded for the first time at the meeting of the German Urological Association in Hamburg in 1990. The prize, which will be donated by Karl Storz Ltd, will amount to öS 50,000 and will be awarded biennially for the best paper in the field of reconstructive surgery in urology or endourology. The award may be split.

Papers may be written in either German or English and should be submitted in triplicate to Dr H. Fuchshuber, Adamgasse 15, A-6020 Innsbruck, by 1 March 1990.

A code word should be affixed to each manuscript, which should not bear the author's name. In a separate envelope bearing the code word the following information should be given: author's first name, surname, position, and code word.

First International Workshop and Symposium on New Urological Technology

Leuven, Belgium. 6–9 September 1989

Further information from: N.U.T. Congress Secretariat, Mrs M. Peeters, Department of Urology, U.Z. Leuven, Brusselsestraat 69, B-3000 Leuven, Belgium.

Annual Meeting of the Swiss Society of Urology

Aarau, Switzerland. 21–23 September 1989

The main themes will be Renal Carcinoma and Ultrasound in Urology.

Further information from: Professor R. Tscholl, Urologische Klinik, Kantonsspital, CH-5001 Aarau, Switzerland, or Professor D. Hauri, Urologische Klinik, Universitätsspital, CH-8091 Zürich, Switzerland.

XXIII Annual Conference of the Urological Society of India

Ahmedabad, India. 21–25 September 1989

Further information from: Dr P. C. Patel, Organising Secretary, Dhananjay Nursing Home, Near Nagri Hospital, Ellisbridge, Ahmedabad 380 006, India.

Fourth Steglitz Pediatric Surgical Symposium: Laser Application in Children

Berlin, West Germany. 10 and 11 November 1989

Further information from: Dr Felix Schier, Department of Pediatric Surgery, Free University of Berlin, Hindenburgdamm 30, 1000 Berlin 45, West Germany.

Second European Symposium on Stone Disease

Basel, Switzerland. 22–24 March 1990

Further information from: Mrs W. Heinzelmann, Urologische Klinik, Departement Chirurgie der Universität Basel, Spitalstrasse 21, CH-4031 Basel, Switzerland.

Second Copenhagen Symposium on Uroradiology

Herlev, Denmark. 27–30 August 1990

The following topics will be included: Upper urinary tract imaging and intervention; Contrast medium nephrotoxicity; Hydronephrosis/obstruction; The urinary bladder; Genital radiology; The adrenal glands; Free communications.

International Continence Society: 20th Annual Meeting

Aarhus, Denmark. 12–15 September 1990

Further information from: Dr J. P. Nørgaard, Institute of Clinical Experimental Research, University of Aarhus, DK-8000 Aarhus C, Denmark.

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A Prospective Study of the Value of Conventional CT, Dynamic CT, Ultrasonography and Arteriography for Staging Renal Carcinoma

N. J. M. LONDON, N. MESSIOS, R. B. KINDER, J. G. SMART, D. E. OSBORN, E. M. WATKIN and J. T. FLYNN

Departments of Urology and Radiology, Leicester General Hospital, Leicester

Summary—The value of dynamic CT scanning for staging renal carcinoma was studied prospectively in 28 patients and the results compared with those of ultrasonography, arteriography and conventional CT. Arteriography correctly staged 48% of tumours; ultrasonography and conventional CT correctly staged 50% and dynamic CT correctly staged 72%.

Dynamic CT staged renal carcinoma more accurately than ultrasonography, conventional CT or arteriography and it is suggested that arteriography should be restricted to specific indications such as the mapping of arterial anatomy and therapeutic renal artery embolisation.

The mortality rate from renal carcinoma in England and Wales has continued to rise since 1951 (Toms *et al.*, 1981). The major determinant of the prognosis for patients with this tumour is the stage at presentation (Skinner *et al.*, 1971; Golimbu *et al.*, 1986) and the staging system most commonly used is that described by Robson *et al.* (1969). It has become apparent that those patients with stage 3 disease who have renal vein involvement only (Skinner *et al.*, 1971; Golimbu *et al.*, 1986) and those with vena caval and renal vein involvement only (Cherrie *et al.*, 1982; Libertino *et al.*, 1987; Selli *et al.*, 1987) can with appropriate surgical treatment achieve a 5-year survival equal to that of stage 1 patients. In contrast, patients with lymph node metastases only or lymph node and venous invasion have a uniformly poor prognosis (Skinner *et al.*, 1972; Scheffit *et al.*, 1978; Waters and Richie, 1979; McNichols *et al.*, 1981; Bassil *et al.*, 1985).

Accurate pre-operative staging of renal carcinoma allows the surgeon to plan his operative approach and is invaluable when the inferior vena cava is involved and exploration of that vessel is required, including (if necessary) circulatory arrest and cardiopulmonary bypass (Libertino *et al.*, 1987; Montie *et al.*, 1988). Accurate tumour staging also allows non-operative treatment to be offered to those patients who fall into a poor prognosis group and are unfit or unsuitable for surgery (Dekernion *et al.*, 1978; Best, 1987). The methods used to stage renal carcinoma have included infusion nephrotomography (Evans *et al.*, 1954), selective renal arteriography and pharmaco-angiography (Kahn *et al.*, 1968), inferior vena cavography (McCoy *et al.*, 1969), lymphangiography (Carl *et al.*, 1977), intravenous digital subtraction angiography (Ford *et al.*, 1985), conventional CT (Levine *et al.*, 1979), dynamic CT (Lang, 1984a), radionuclide scanning (Cole *et al.*, 1975), ultrasonography (Green *et al.*, 1979) and nuclear magnetic resonance imaging (Hricak *et al.*, 1985; Strake *et al.*, 1988).

The purpose of this prospective study was to compare the results of tumour staging by dynamic CT with the results of staging by ultrasonography, arteriography and conventional CT.

Patients and Methods

Between December 1985 and December 1987, patients with solid renal masses on ultrasonography were referred for selective renal arteriography, conventional CT and dynamic CT. Inferior vena cavography was done only if there was a specific

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Accepted for publication 19 December 1988

indication. These investigations were reported "blind" by a consultant radiologist who recorded on a standard proforma the presence or absence of extracapsular tumour spread, local or regional lymphadenopathy and renal vein or inferior vena cava tumour extension.

The ultrasound examinations were performed with a Picker LSC 7000 real time scanner using a 3.5 MHz curved linear array transducer. Selective renal arteriography was performed using a percutaneous transfemoral Seldinger technique with renal artery injection of Niopam 300. CT examinations were done on an IGE 8800 scanner. After a conventional pre-enhancement CT scan using a slice thickness of 10 mm, slice interval of 10 mm and scan time of 8 s, the dynamic scan was started half-way through a 100 ml intravenous infusion of Niopam 370. The Niopam 370 was administered through an anticubital vein. The dynamic scan took rapid sequence 10 mm contiguous sections through the kidneys with a scan time of 4.0 s and interval between scans of 2.4 s (for table movement). Finally, a conventional post-enhancement scan was obtained 5 min after the intravenous injection of contrast. This scan used the same scan time, section thickness and slice interval as the pre-enhancement scan. The term "conventional CT" is used in this report to refer to the pre- and post-enhancement scans.

Pathological staging was determined histologically from tissue obtained at operation, autopsy or Tru-cut biopsy. The staging system used was that described by Robson *et al.* (1969) (Table 1). Diagnostic accuracy, sensitivity and specificity were calculated as described by McNeil *et al.* (1985). Discrete variables were analysed by the chi-squared test with Yates' correction when the expected number of observations was small. Statistical significance was assumed to be $P < 0.05$.

Table 1 Staging System for Renal Carcinoma (Robson *et al.*, 1969)

Stage 1
Confined to kidney

Stage 2
Extracapsular spread, *i.e.* perirenal fat involvement but confined to Gerota's fascia

Stage 3
Involvement of renal vein, inferior vena cava or regional lymph nodes

Stage 4
Invasion of adjacent organs other than adrenal gland, or distant metastases

Table 2 Details of 28 Patients with Renal Carcinoma

Male	21* (75)
Female	7 (25)
Median age (range) (years)	64 (43–83)
Side of tumour	
Right	17* (61)
Left	11 (39)
Number of patients with:	
Extracapsular spread	7* (25)
Lymph node metastases	10 (36)
Renal vein invasion	11 (39)
Vena cava invasion	3 (11)
Pathological stage of tumour	
Stage 1	9* (32)
Stage 2	0 (0)
Stage 3	14 (50)
Stage 4	5 (18)

* Figures in parentheses are percentages

Results

A total of 33 patients with solid renal masses on ultrasonography was referred for dynamic CT scanning during the 24-month study period; 28 of these patients were staged pathologically. Pathological staging was based on histological examination of an operative specimen in 23 patients, autopsy material in 3 and Tru-cut biopsy in 2. The age–sex distribution and pathological stage of these 28 patients is given in Table 2. All patients underwent conventional CT and dynamic CT. Arteriography was performed in 24 patients but had to be abandoned in 3 due to back pain; 10 patients underwent inferior vena cavography.

The results of tumour staging by ultrasonography, conventional CT, dynamic CT and arteriography with respect to extracapsular spread, lymph node metastases, renal vein and inferior vena cava invasion are given in Tables 3, 4, 5 and 6 respectively. All of the CT and arteriogram examinations were technically satisfactory. Ultrasonography, however, did not adequately display the renal vein in 15/28 patients (54%) or the inferior vena cava in 6/28 (21%). The overall staging accuracy of ultrasonography, conventional and dynamic CT and arteriography is documented in Table 7.

Inferior vena cavography, which was performed in 10 patients, correctly identified normal venous anatomy in 4 patients, detected renal vein tumour extension in 4 and vena cava invasion in 1. There was 1 false positive for vena cava tumour invasion.

Table 3 Results of Detection of Extracapsular Tumour spread (ECS) by Ultrasonography, Conventional CT, Dynamic CT and Arteriography

	ECS, n=7			*ECS, n=3*
	Ultrasonography (n=28)	*Conventional CT (n=28)*	*Dynamic CT (n=28)*	*Arteriography (n=21)*
True +ve	1	2*	7*	2
True −ve	20	21	20	14
False +ve	1	0	1	4
False −ve	6	5	0	1
Sensitivity (%)	14	28	100	66
Specificity (%)	95	100	95	78
Diagnostic accuracy (%)	75	82	96	76

* $P<0.05$, X^2

Table 4 Results of Detection of Lymph Node Metastases (LNM) by Ultrasonography, Conventional CT, Dynamic CT and Arteriography

	LNM, n=10			*LNM, n=6*
	Ultrasonography (n=28)	*Conventional CT (n=28)*	*Dynamic CT (n=28)*	*Arteriography (n=21)*
True +ve	4	6	8	0
True −ve	18	17	17	15
False +ve	0	1	1	0
False −ve	6	4	2	6
Sensitivity (%)	40	60	80	0
Specificity (%)	100	94	94	100
Diagnostic accuracy (%)	79	82	89	71

Table 5 Results of Detection of Renal Vein Invasion (RVI) by Ultrasonography, Conventional CT, Dynamic CT and Arteriography

	RVI, n=11			*RVI, n=10*
	Ultrasonography (n=28)	*Conventional CT (n=28)*	*Dynamic CT (n=28)*	*Arteriography (n=21)*
True +ve	2	0*	9*	0
True −ve	16	17	13	11
False +ve	1	0	4	0
False −ve	9	11	2	10
Sensitivity (%)	18	0	82	0
Specificity (%)	94	100	76	100
Diagnostic accuracy (%)	64	61	79	52

* $P<0.0001$, X^2

Discussion

The age–sex distribution and tumour stage at presentation in this study are similar to those of other studies from both the UK (Best, 1987) and the USA (Skinner *et al.*, 1971; Golimbu *et al.*, 1986). This suggests that the patients in our study were representative of those seen by most departments of urology. The system of staging renal carcinoma described by Robson *et al.* (1969) has been widely adopted and we have used that classification for this study so that the results may be compared with those of previous authors.

The first report of the staging of renal carcinoma by conventional CT came from Levine *et al.* (1979). Love *et al.* (1979) were the first authors to use

Table 6 Results of Detection of Inferior Vena Cava Invasion (IVCI) by Ultrasonography, Conventional CT, Dynamic CT and Arteriography

	IVCI, n=3			*IVCI, n=1*
	Ultrasonography (n=28)	*Conventional CT (n=28)*	*Dynamic CT (n=28)*	*Arteriography (n=21)*
True +ve	1	0	2	0
True −ve	25	25	23	20
False +ve	0	0	2	0
False −ve	2	3	1	1
Sensitivity (%)	33	0	66	0
Specificity (%)	100	100	92	100
Diagnostic accuracy (%)	93	89	89	95

Table 7 Overall Staging Accuracy of Ultrasonography, Conventional CT, Dynamic CT and Arteriography

	Ultrasonography (n=28)	*Conventional CT (n=28)*	*Dynamic CT (n=28)*	*Arteriography (n=21)*
Pathological staging				
Correct	14 (50)	14 (50)	20 (72)	10 (48)
Understaged	14 (50)	13 (46)	4 (14)	11 (52)
Overstaged	0 (0)	1 (4)	4 (14)	0 (0)

Figures in parentheses are percentages.

dynamic CT for the staging of renal carcinoma and the technique has since been described in detail by Lang (1984a). The dynamic CT scan consists of a series of rapid sequence contiguous cuts taken during the intravenous infusion of contrast medium. Normal renal parenchyma enhances as contrast material passes through the arteriolar, capillary and venous phases of the circulation. Because the majority of renal carcinomas are well vascularised (Blath *et al.*, 1976), they also enhance during the dynamic CT scan (Figs 1 and 2). This positive enhancement facilitates the detection of tumour spread into the perirenal spaces and adjacent organs (Fig. 3). Arterialised tumour thrombus within the renal vein or inferior vena cava can be detected by enhancement during the capillary phase of the dynamic scan or as filling defects during the venous phase (Figs 4 and 5). Similarly, tumour deposits within local or regional lymph nodes can be detected by their enhancement during the capillary phase of the dynamic CT scan (Fig. 6). The conventional post-enhancement scan at 5 min is in effect a "CT nephro-pyelogram". Because renal carcinomas do not contain functioning tubular tissue they do not enhance during this scan. This lack of enhancement reduces the value of a conventional post-enhancement scan for the delineation of tumour spread.

Although there have been previous studies of the staging of renal carcinoma by ultrasonography, the majority have examined a single staging criterion such as venous tumour extension (Schwerk *et al.*, 1985) or the "T" stage (Frohmuller *et al.*, 1987). Cronan *et al.* (1982) looked at overall tumour staging by ultrasonography and found it to have an accuracy of 70% (16 of 23 patients). Lang (1984b) did not produce a figure for the overall staging accuracy of ultrasonography but did examine the accuracy of ultrasonography for detecting individual staging criteria. The results of his study were remarkably similar to our own and we would agree that the diagnostic contribution of ultrasonography is marred by a large number of false negative and false positive results for each stage of the disease.

One of the reasons for the poor performance of ultrasonography is the difficulty of identifying retroperitoneal structures, particularly hilar lymph nodes, the renal veins and the infrahepatic vena cava. We found that the visualisation of the renal veins and vena cava was inadequate in 54% and 21% of patients respectively. The corresponding figures from Webb *et al.* (1987) are 75% and 64% and from Schwerk *et al.* 1985) 34.2% and 4.2%. Levine *et al.* (1980) found that it was not possible to distinguish between stage 1 and stage 2 tumours by ultrasonography and that failure to visualise the

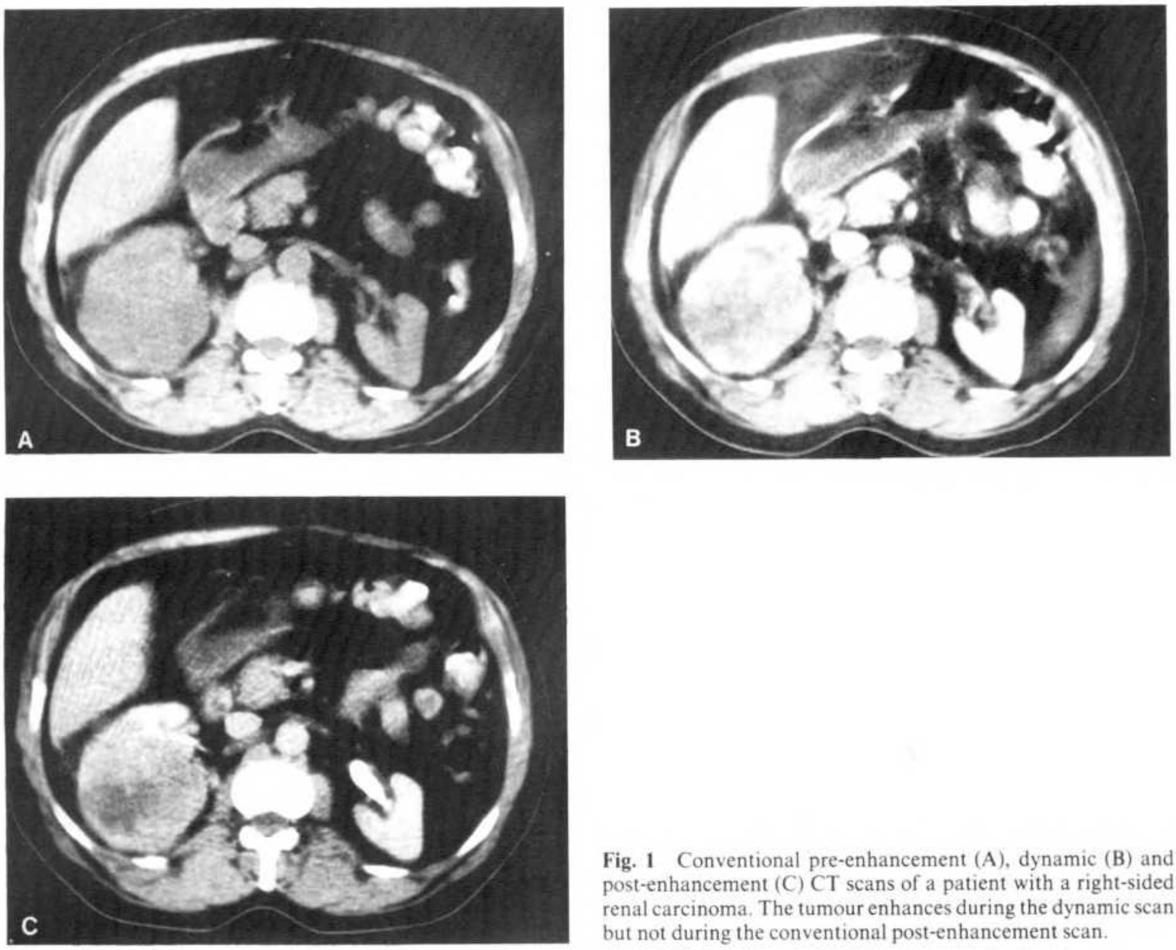

Fig. 1 Conventional pre-enhancement (A), dynamic (B) and post-enhancement (C) CT scans of a patient with a right-sided renal carcinoma. The tumour enhances during the dynamic scan but not during the conventional post-enhancement scan.

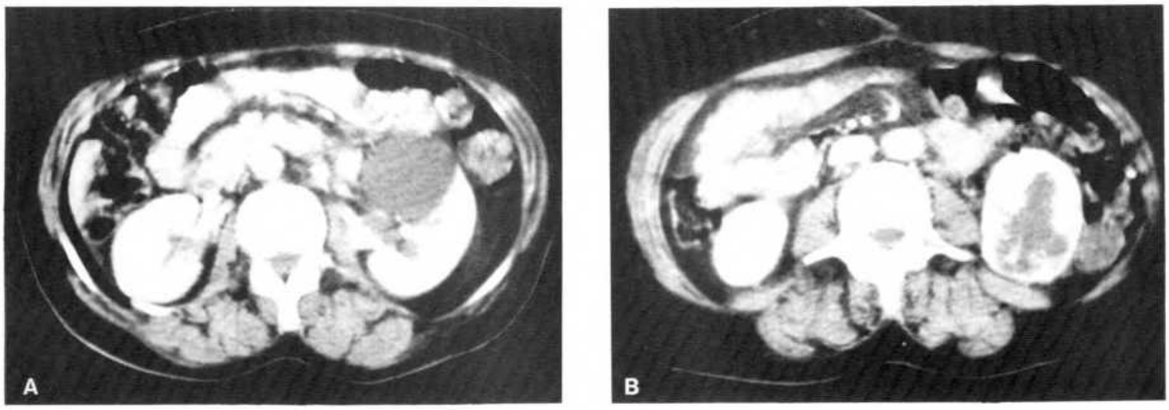

Fig. 2 Dynamic CT scans of a patient with a simple renal cyst superiorly (A) and renal carcinoma inferiorly (B) in the left kidney. The simple renal cyst does not enhance during the dynamic scan whereas the renal carcinoma does enhance.

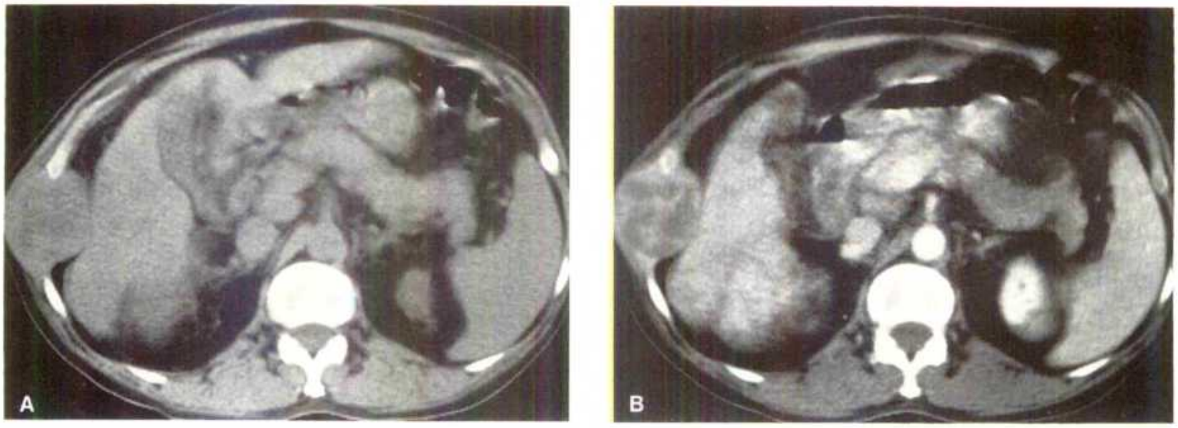

Fig. 3. Conventional pre-enhancement (A) and dynamic CT scan (B) of a patient with a right-sided renal carcinoma that has invaded the rib cage. Note that the tumour extension into the rib cage enhances during the dynamic scan.

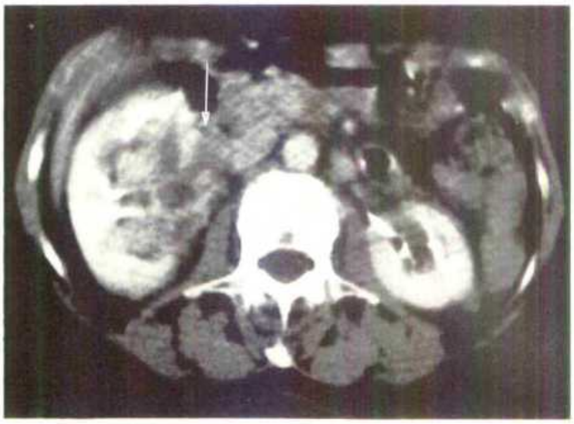

Fig. 4 Venous phase dynamic CT scan of a right-sided renal carcinoma that has invaded the renal vein. The tumour thrombus is seen as a filling defect (arrow) within the origin of the renal vein.

renal veins or retroperitoneum in 50% of patients made correct delineation of stage 3 patients difficult.

We found selective renal arteriography to be the least accurate method of pre-operative tumour staging. This finding is in agreement with previous reports (Weyman *et al.*, 1980; Probst *et al.*, 1981; Cronan *et al.*, 1982). The accuracy of selective renal arteriography for "T" staging alone is around 60% (Das *et al.*, 1977; Frohmuller *et al.*, 1987), although this figure may be improved upon with the use of pharmaco-angiography (Lang, 1973). The major source of error from angiography arise from the fact that retroperitoneal or capsular collaterals may be demonstrated when the renal capsule is still intact (Probst *et al.*, 1981) and that the demonstration of tumour neovascularity in an enlarged node is inconsistent and subject to confusion with tumour thrombus in the renal vein (Lang, 1984b). Inferior

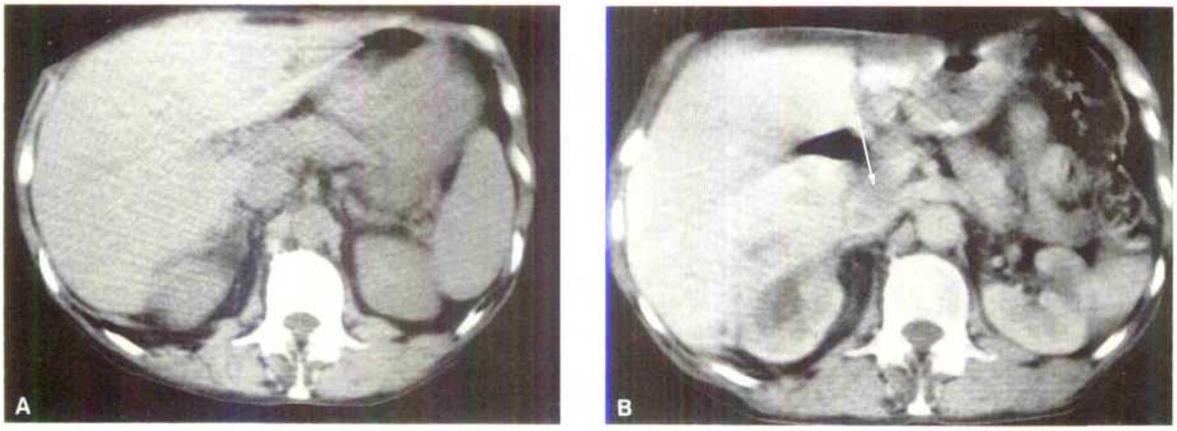

Fig. 5 Conventional pre-enhancement (A) and dynamic CT scan (B) of a patient with a right-sided renal carcinoma. It can be seen from the dynamic scan that there is tumour thrombus within the vena cava (arrow); this is not apparent from the conventional scan.

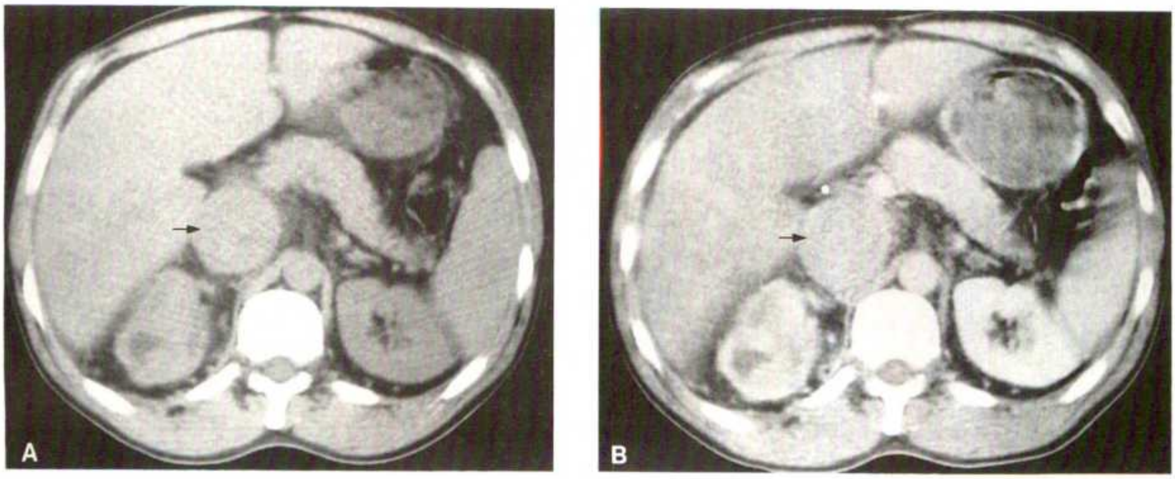

Fig. 6 Conventional pre-enhancement (A) and dynamic CT scan (B) of a right-sided renal carcinoma with a mass of lymph nodes anterior to the inferior vena cava (arrow). These lymph nodes enhance during the dynamic scan, confirming that they contain metastatic tumour.

vena cavography had an accuracy of 90% for demonstrating the state of the inferior vena cava and renal veins in the present study, a figure very close to the accuracy of 86% reported by Siminovitch *et al.* (1982). There was 1 false positive for vena caval tumour extension; this resulted from flow artefact within the retrohepatic vena cava, a well recognised source of error (Siminovitch *et al.*, 1982). It has been suggested by Ford *et al.* (1985) that intravenous digital subtraction angiography can provide the same information as inferior vena caveography, but in a less invasive manner.

The reported accuracy of CT for the staging of renal carcinoma has ranged from 61 to 91% (Table 8). Many of these studies are retrospective and have not compared the results of staging by conventional CT with dynamic CT. Although Lang (1984b) compared the results of pre-operative staging by conventional CT with dynamic CT he did not produce a figure for the overall accuracy of these investigations. We have found that dynamic CT performed better than conventional CT for the assessment of extracapsular spread, renal vein invasion and vena cava invasion. The reasons for the superior performance of dynamic CT are that the positive enhancement of abnormal tissue allows accurate assessment of tumour spread, and that the late phase of the dynamic scan defines the venous anatomy more clearly than conventional CT. There is scope for improvement of the results of staging by dynamic CT in the assessment of vena cava tumour extension. We are at present investigating whether dynamic CT scans performed with contrast injection via the femoral vein, thereby providing a "CT cavogram", improve on the results of staging by dynamic CT with contrast injection via an antecubital vein.

Table 8 Accuracy of CT for Staging Renal Carcinoma

Authors	*Year*	*No. of patients studied*	*Accuracy (%)*
Love *et al.*	1979	17	89
Probst *et al.*	1981	40	85
Karp *et al.*	1981	27	70
Cronan *et al.*	1982	23	91
Plainfosse *et al.*	1983	12	75
Elder *et al.*	1984	31	62
Rinsho *et al.*	1987	34	82
Fein *et al.*	1987	27	67
Kishi *et al.*	1987	18	61
Johnson *et al.*	1987	100	91
McKinstry and McIlrath	1987	21	78

We were unable to compare magnetic resonance imaging (MRI) with dynamic CT. Three recent reports have, however, shown that MRI has a staging accuracy similar to that of CT (Fein *et al.*, 1987; Kishi *et al.*, 1987; Strake *et al.*, 1988) and conclude that CT remains the method of choice for staging renal carcinoma.

The results of our study show that dynamic CT stages renal carcinoma more accurately than conventional CT, ultrasonography or arteriography. It is concluded that dynamic CT is the best method available for the staging of renal carcinoma and that arteriography should be restricted to specific indications such as the mapping of arterial anatomy and therapeutic renal artery embolisation.

Acknowledgement

We are grateful to Mrs Denise Jarvis for secretarial assistance.

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Cyclic Interferon Gamma Treatment of Patients with Metastatic Renal Carcinoma

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Summary—The treatment of metastatic renal carcinoma is still unsatisfactory because of the lack of effective systemic therapy. In 14 patients with metastatic renal carcinoma an attempt was made to influence the course of the disease by administration of recombinant human interferon (rHu-IFN) gamma; 9 patients were evaluated after treatment.

There was partial remission in 3 patients, stable disease in 2 and tumour progression in 4. The cyclic application of rHu-IFN at a dose of 0.25 mg/day for 8 days, with treatment-free intervals of 3 to 4 weeks, was tolerated well. Side effects consisted mainly of fever and leucocytopenia. From this small series it seems that cyclic IFN gamma treatment might be helpful in some cases of metastatic renal carcinoma.

The treatment of metastatic renal carcinoma remains unsuccessful. A study was undertaken to assess the effect of cyclic immunotherapy with recombinant human interferon gamma. It has been shown that human interferon (IFN) and other "biological response modifiers" produce promising results. It has not yet been established which treatment schedule, route of application and dose of interferon are most suitable in the treatment of patients with metastatic renal carcinoma. Our studies of the long-term application of IFN alpha-2c have shown that this schedule does not result in permanent immunological stimulation. When augmentation of natural killer (NK) cell activity by interferon treatment has occurred, long-term application does not lead to further stimulation of the NK cell system (Grups *et al.*, 1985) and it was therefore decided to use repeated short-term courses of treatment with IFN.

Patients and Methods

Between June 1986 and April 1988, 14 patients with metastatic renal carcinoma were treated systemically with rHu-IFN gamma. In 12 of these patients nephrectomy had already been carried out. In 2 patients whose general condition was poor, surgical removal of the tumour was not feasible. The metastases had been confirmed histologically by biopsy in 4 patients. In the remaining 10, metastatic spread was verified by 2 imaging methods. With one exception, no patient had received prior radiotherapy, chemotherapy or hormonal treatment. The tumour stages and Karnofsky index of the 9 patients evaluated after treatment are shown in Table 1.

After giving informed consent, patients received daily intramuscular injections of 0.25 mg rHu-IFN gamma for 8 days. The interferon (provided by Boehringer, Ingelheim, FRG) had a 98% degree of

Table 1 Tumour stage and Karnofsky Index after Treatment with Cyclic Interferon Gamma

Patient no.	*Age (years)*	*Tumour stage*			*Karnofsky index*
1	66	pT3	pNO	M1	90
2	44	pT2	pNO	pM1	70
3	43	pT3	pN2	M1	70
4	56	pT3	pNO	pM1	70
5	53	pT3	pNO	M1	80
6	49	pT3	pNO	M1	90
7	36	pT3	pNO	pM1	100
8	62	pT3	pN2	M1	80
9	61	pT3	pNO	M1	90

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purity and specific activity of 2×10^7 IU/mg protein. Between each 8-day period there was a treatment-free interval of 3 to 4 weeks. Some patients received up to 11 cycles of treatment.

Results

The effectiveness of treatment was assessed according to WHO criteria in 9 of the 14 patients. In the remainder the duration of treatment was inadequate.

Stable disease was noted in 2 patients and partial remission of tumour in 3, 2 of whom had pulmonary metastases and 1 a solitary metastasis in the left os ileum. In 1 of the 2 patients with pulmonary metastases, multiple metastases in both lungs disappeared almost completely. After 6 treatment cycles only 2 small residual lesions were seen, but despite further IFN gamma treatment they did not disappear completely. In the second patient with a pulmonary metastasis there was a 50% reduction in tumour volume. Recalcification of the osteolysis was noted in the patient with a bony metastasis and he reported complete relief of pain. Progression of disease was noted in 4 patients. After undergoing 1 IFN gamma treatment cycle, 2 patients died of unrelated causes. One male patient died of an acute aortic aneurysm and a female suffered a fatal pulmonary embolism 28 days after finishing the first treatment cycle. The results in the remaining 9 patients are shown in Table 2.

During systemic treatment with rHu-IFN gamma, all patients developed influenza-like symptoms. Fever (up to 39.5°C), occasional shivering and limb pain were the most frequent clinical symptoms. Laboratory tests showed no significant changes other than leucocytopenia. The symptoms became apparent approximately 2 h after the injection of rHu-IFN gamma and reached their peak 4 to 5 h later; they then regressed over the next few hours. At the end of IFN treatment the leucocyte counts rose again and became completely normal in all cases. Liver tests showed no changes associated with treatment. Superficial thrombosis in the legs occurred in 2 patients.

Table 2 Results of Cyclic Treatment with rHu IFN Gamma

Patient no	*Metastases*	*IFN cycles*	*Result*	*Duration (months)*
1	Lungs	11	PR	18
2	Bones	9	PR	10
3	Lungs	5	PR	4
4	Bones	8	SD	14
5	Lungs	8	SD	8
6	Lungs	10	Progression	—
7	Bones	8	Progression	—
8	Lungs/bones	8	Progression	—
9	Lungs	6	Progression	—

PR: Partial remission.
SD: Stable disease.

Discussion

In view of the advanced tumour stage and poor prognosis of these patients, the present results are encouraging. Since complete remission of tumour could not be achieved, it is evident that cyclic treatment with IFN gamma is merely palliative. A reason for the partial response of metastases might be found in the polyclonal origin of the tumour. In addition, the dosage of IFN may not have been optimal in every case. Kirkwood *et al.* (1985) showed that treatment with high dose IFN alpha led to improved results in renal carcinoma compared with low dose IFN treatment. It remains debatable whether these results can be translated into an effective form of treatment with IFN gamma.

Patients with metastatic renal carcinoma often seek further treatment despite having distant metastases and a poor prognosis, and treatment with IFN could be regarded as an extension of therapy. A review of the literature by Neidhart (1986) revealed that response rates of 14 to 20% could be reached with IFN treatment in metastatic renal carcinoma; the comparable rates for chemotherapy were 9 to 17% and for hormonal therapy only 0.8 to 6%.

As noted earlier, a major problem of IFN treatment of solid tumours is that the optimal dosage and application schedules have not yet been established. The question of whether it is better to have high IFN serum levels over a short period of time by means of intravenous administration also remains unanswered (Kurzrock *et al.*, 1985). Despite these problems, the potential benefits of IFN therapy (perhaps combined with cytotoxic agents) in the treatment of renal carcinoma deserve further investigation. Balkwill and Moodie (1984) reported synergistic effects of IFN and chemotherapeutic agents, but there is controversy over whether IFN treatment can prolong the actuarial survival time (Quesada *et al.*, 1985; Umeda and Niijma, 1986). One of our patients suffered a fatal pulmonary embolism and 2 developed superficial thromboses but these events did not appear to be related to IFN treatment. There is no suggestion that IFN gamma treatment leads to a higher risk of coagulation disorders (Kurzrock *et al.*, 1985), although it is known that there is an association between progression of carcinoma and clot formation. Tumour cells have the ability to aggregate platelets and to convert fibrinogen to fibrin (Zacharski, 1987). Since the side effects of IFN treatment are minimal and since it may be carried out on an out-patient basis, it is feasible to assess a larger number of patients. In oncology, better results are achieved when treating small tumours and consideration should be given to the administration of IFN as adjuvant treatment after tumour nephrectomy if extensive lymph node metastases are present, since a high rate of tumour progression is to be expected in these patients (Williams *et al.*, 1984).

The cost of cyclic interferon gamma treatment cannot be compared with that of interferon alpha since the drug is available for clinical trials only.

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Maps for Diagnosis and Management of Antenatal Urinary Tract Dilatation

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Summary—Despite advances in radiological imaging techniques, the ideal management of antenatally diagnosed hydronephrosis remains controversial. A map, showing diagnostic and management pathways, has been designed in an attempt to provide maximum information from the most appropriate and minimum number of investigations.

Fetal imaging with ultrasound is now a routine investigation in early pregnancy both for accurate dating and screening for fetal anomalies in several systems. Dilatation of the urinary tract can be detected as early as 16 weeks and by 18 to 20 weeks, in the presence of bilateral dilatation and a distended bladder, urethral outflow obstruction can be suspected (Gray and Crane, 1988). Approximately 1 in 500 fetal scans shows urinary tract dilatation (Helin and Persson, 1986; Colodny, 1987).

Aims

The main aim is to detect anomalies sufficiently early so that a team of specialists (urologist, radiologist and paediatrician) can be alerted to take appropriate action as soon as the child is born (Turnock and Shawis, 1984; Smith *et al.*, 1987). In rare cases it may be appropriate to treat the fetus before birth by antenatal intervention or even to abort the fetus if severe enough anomalies are found sufficiently early in pregnancy (Harrison *et al.*, 1982a and b; Manning, 1987; Reuss *et al.*, 1988a and b).

Most of the clinically significant anomalies are associated with either reflux or obstruction, both of which produce dilatation. A third explanation for dilatation is urinary tract dysplasia, where there may be neither reflux nor obstruction (Blane *et al.*, 1983). An early definitive diagnosis can lead to appropriate treatment, usually after the birth of the child, with the obvious advantage that nephron function can be preserved and the scarring of reflux nephropathy prevented.

Pitfalls

Although the benefits seem clear, the detection and management of dilatation is not quite as straightforward as it might seem (Thomas *et al.*, 1985). Errors in diagnosis and interpretation of dilatation are common; not only may the incorrect diagnosis within the urinary tract be made but the apparent "dilatation" may not be in the urinary tract at all (Avni *et al.*, 1985; Reuter and Lebowitz, 1985; Madarikan *et al.*, 1988). Furthermore, dilatation may not be significant; in 25% of cases the urinary tract is found to be within normal limits on re-investigation at birth, or there is a genuine improvement in dilatation on later ultrasound (Degani *et al.*, 1988; Scott and Renwick, 1988).

Dilatation associated with dysplasia is usually best left alone, as misguided interpretation may lead to inappropriate surgery. Major chromosomal abnormalities, rendering the fetus non-viable, may occasionally be associated with dilatation and clearly it would be unwise to treat the urinary tract until these have been clarified. Diagnostically, much depends on the amount of amniotic fluid and before 20 weeks this estimation is somewhat subjective. After 24 weeks the amount of fluid is easier to quantify.

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Antenatal Intervention

Despite considerable experience in some centres, the place of antenatal intervention remains uncertain. All agree that there is no place for drainage of a unilateral hydronephrosis where there is a normal opposite kidney. It may be appropriate to drain the urinary tract in the presence of oligohydramnios with severe, progressive, bilateral obstruction as, for instance, in a boy with a posterior urethral valve, but there are little if any data to substantiate the advantages of this treatment (Elder *et al.*, 1987; Reuss *et al.*, 1988a and b; Sholder *et al.*, 1988). Fortunately, this set of circumstances occurs in only 1% of all cases of fetal urinary tract dilatation (Colodny, 1987).

Methods of investigation

Ultrasound (U/S). Antenatally, ultrasound can detect changes in the amount of amniotic fluid, can document the growth of the child and follow dilatation of the urinary tract. In the first few days after birth the urinary output increases markedly in the infant, so that a relatively normal scan at birth may be abnormal 4 to 5 days later (Laing *et al.*, 1984). A search should be made for a full ureter behind the bladder, signifying either lower ureteric obstruction or reflux. In the latter it may only be seen with a full bladder. The thickness of the bladder wall and the bladder's ability to empty completely can be judged with ultrasound. In a boy with a posterior urethral valve it may be possible to detect dilatation of the prostatic urethra.

Micturating cystourethrography (MCU). This is the only reliable way of showing vesicoureteric reflux in the neonate and infant. The alternatives of indirect or even direct radioisotope cystography in this age group are unsatisfactory because of the close proximity of the kidneys and bladder. Although a posterior urethral valve may be suspected clinically, only micturating cystography can image it satisfactorily. Antibiotic cover is advisable as the introduction of infection is a real risk.

^{99m}Tc *Diethylenetriamine pentacetic acid (DTPA) scintigram.* This is a dynamic scan that gives relative function, transit rate through the kidney and information about drainage. Since glomerular filtration and glomerular blood flow are still low in the neonate, the handling of the isotope is unpredictable and possibly misleading. Even a normal kidney may give an abnormal scan. Assessment of differential function is accurate at 4 to 6 weeks and after 2 to 3 months the drainage curves can be useful in the detection of obstruction (Gordon, 1985). A diuretic may be needed to help to distinguish between stasis alone and stasis from obstruction. The bladder should be draining freely during the study via a urethral catheter so that drainage through the lower ureters can be assessed more efficiently.

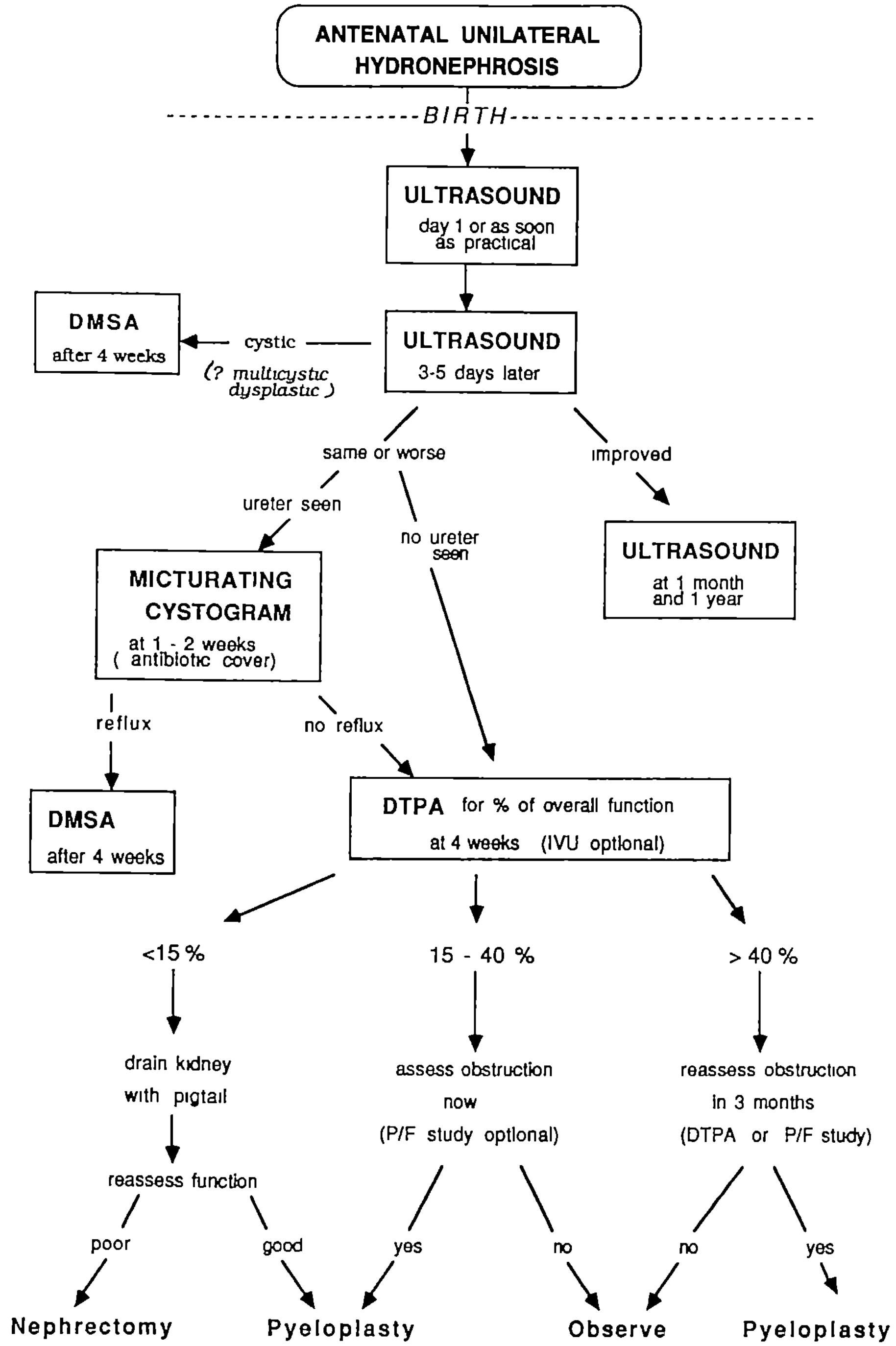
^{99m}Tc *Dimercaptosuccinic acid (DMSA) scintigram.* This is a static scan that shows the renal morphology. It is the best method of demonstrating the scars of reflux nephropathy (Verber *et al.*, 1988) and the absence of function in a multicystic kidney. The immature renal tubules retain the compound less well and there is some leaking of the isotope into the bladder or even, in the presence of reflux, into the contralateral kidney and this may give a misleading estimation of function (Gordon, 1985). After 4 weeks of age the scan becomes more accurate and useful.

Intravenous urography (IVU). Neonatal kidneys handle contrast medium poorly and imaging by this technique is generally unsatisfactory in this group. The osmotic load of a bolus of contrast medium can also be hazardous. There are times, however, when the morphological information provided by an IVU is needed as, for instance, in the presence of a duplex kidney with a ureterocele or other type of ectopic ureter.

Specific conditions

Hydronephrosis (pelviureteric junction obstruction). Unilateral hydronephrosis is the most common cause of a dilated urinary tract in a prenatal scan (Colodny, 1987). It is clear that many of these cases improve spontaneously but even if there is a definite obstruction, as shown by renography or pressure-flow study (P/F), there is probably no need for immediate action as the obstruction has already been present for several months. Map 1 shows how these are best investigated.

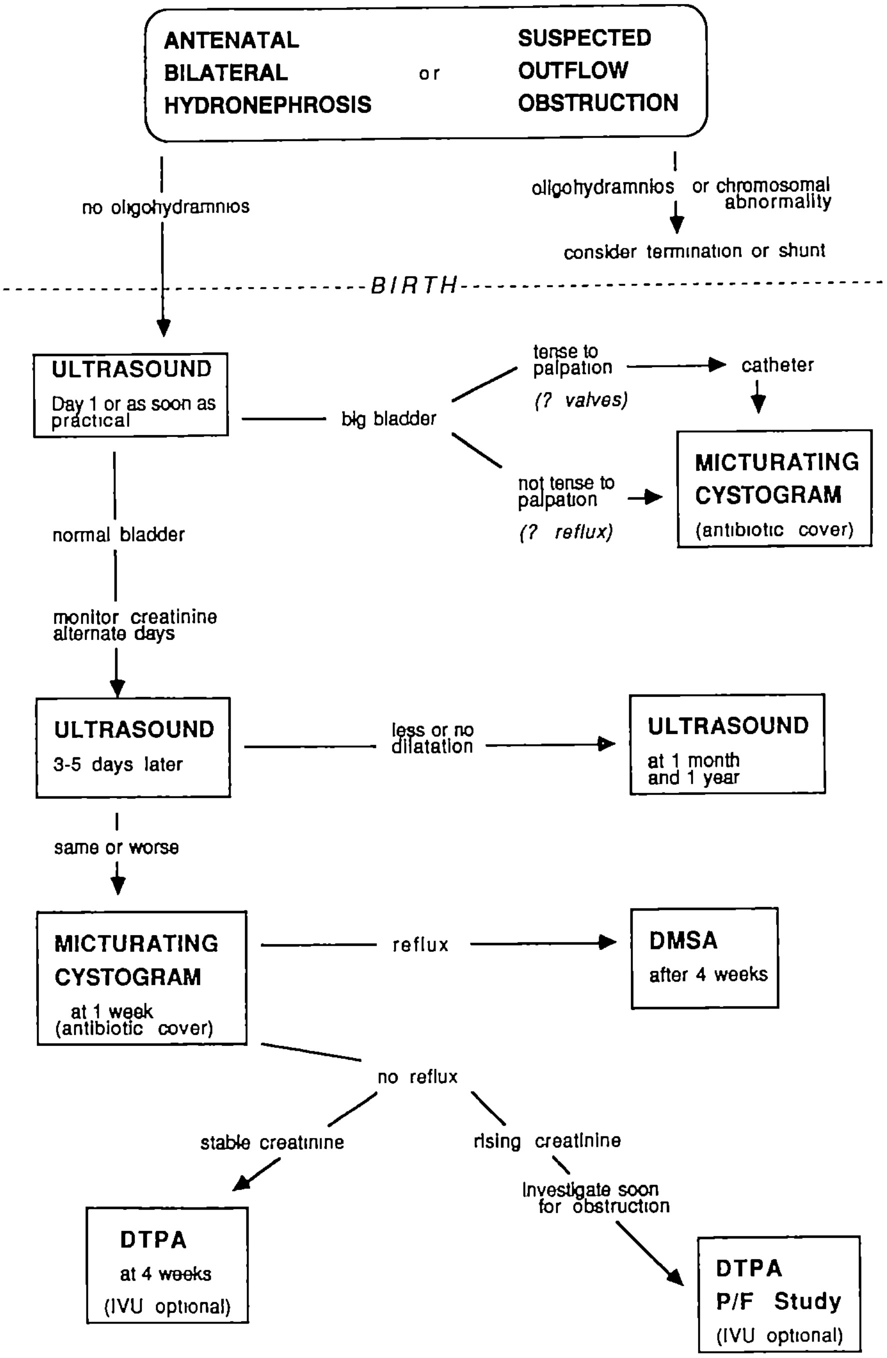
Vesicoureteric reflux. Dilatation associated with reflux may be transient and less easy to detect pre- or post-natally. Lower ureteric dilatation is more likely to be seen when the child has a full bladder. Early detection is important as in some children it may be possible to prevent scarring of the kidneys



Map 1

by prompt antibiotic or surgical treatment (Ransley and Risdon, 1981).

Multicystic kidney. This is a common cause of unilateral dilatation. The kidney is cystic and dysplastic with an atretic ureter and can be shown to have no function on a DMSA scan. It is doubtful now if there is any indication for removing such a kidney, unless it is very large, as it will tend to shrink away over months or years (Thomas, 1984).



Map 2

Posterior urethral valve. Although rare, this is the most common form of treatable outflow obstruction in boys. There is dilatation of the whole urinary tract above the posterior urethra and even the dilated posterior urethra itself may be seen antenatally by ultrasound. At birth the bladder should be drained with a small urethral tube and the diagnosis confirmed with micturating cystourethrography.

Other conditions. Megaureter is treated in a similar fashion to hydronephrosis, as it may be obstructed or unobstructed. Surgery may be necessary for the obstructed type and involves reimplantation of the ureter into the bladder. Preliminary drainage in the form of an end ureterostomy may be more appropriate in infants.

Bilateral hydronephrosis or megaureter may lead to poor renal function and should be managed on the lines of Map 2. Most other anomalies need no immediate action but will come to light during the investigative pathway. An exception is an ectopic ureterocele which can obstruct the bladder neck and cause a bladder outflow obstruction. Ultrasound alone often diagnoses this anomaly.

Map 1

Unilateral hydronephrosis may be due to pelviureteric junction obstruction, megaureter or reflux. There should be no oligohydramnios and there is no indication for prenatal intervention.

The degree of dilatation is checked by ultrasound at birth and again 4 to 5 days later, when the urinary volume has increased. If the dilatation lessens, no action is needed and ultrasound can be repeated at intervals as shown on the map. If the ureter is dilated, MCU is needed to prove or exclude reflux.

If reflux is present, the kidney morphology should be looked at with DMSA at 1 month. In the absence of reflux, a DTPA scan is needed to determine differential function which in turn determines the course of action.

Map 2

Bilateral hydronephrosis may be due to bladder outflow obstruction, severe reflux, or bilateral upper tract obstruction from pelviureteric or ureterovesical obstruction. A fourth cause is dysplasia of the urinary tract such as the prune belly syndrome, when there may be severe stasis but not necessarily reflux or obstruction.

Antenatally, the amount of amniotic fluid must be checked regularly and villous biopsy performed if chromosomal abnormality is suspected. Before 24 weeks in the presence of "bright" kidneys on ultrasound, oligohydramnios, major chromosomal anomaly, or fetal urinary sodium of more than 100 mmol/l, termination may need to be considered (Crombleholme *et al.*, 1988). After 24 weeks there may be a place for shunting fetal urine to the amniotic fluid but, although this may help the urinary tract, it may not alleviate the problem of hypoplastic lungs (Manning, 1987). A full discussion of prenatal intervention is outside the scope of this article. At birth the dilatation is confirmed and, if there is an obviously full bladder, action is taken according to Map 2.

If the bladder is normal, renal function is monitored on alternate days and the ultrasound repeated after 3 to 5 days. Improvement of the dilatation allows a conservative approach with regular ultrasound follow-up.

Unchanged or worsening dilatation suggests the need for a micturating cystogram to prove or exclude reflux. In the absence of reflux, the presence of obstruction should be sought with DTPA scanning earlier or later according to the renal function.

We believe that these two maps, covering unilateral and bilateral dilatation of the urinary tract, represent the state of the art and should be adequate guidelines for all those dealing with these problems. However, we accept that flexibility is important and clinical acumen may override the maps at any stage. We believe that no investigation should be done unless it is likely to alter the management or bring the diagnosis nearer.

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Radiological Changes and Circulating Immune Complexes in Patients with Urinary Schistosomiasis

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Summary—The degree of infection and the urographic picture was correlated to the presence and level of circulating immune complexes (CICs) in 69 patients affected by urinary schistosomiasis. Patients were divided into 2 groups: those eliminating less and those eliminating more than 25 eggs/10 ml of urine. Radiological changes in the urinary tract were present in 67% of patients, the most frequent finding being single or multiple filling defects in the bladder. CICs were present in 39 patients. A positive correlation was found between the presence and level of CICs and the output of *Schistosoma haematobium* eggs, as well as between the presence of CIC and single or multiple filling defects of the bladder.

Our findings indicated that CICs were present in patients with urinary schistosomiasis, but the different incidence in patients with a large egg output and radiological filling defects suggests a possible pathogenic role only in the earlier phase of the infection.

There is increasing evidence that circulating immune complexes may be involved in the pathogenesis of human schistosomiasis. A number of reports have demonstrated the presence of granular basement membrane deposits in the renal glomeruli of patients with chronic infection. Immunoglobulins, complement and also parasite antigens have been identified at these sites. Circulating immune complexes have been demonstrated in a number of patients affected by schistosomiasis. Most studies have dealt with hepato-splenic schistosomiasis due to *Schistoma mansoni* (Galvao Castro *et al.*, 1981; Santoro *et al.*, 1981; Stevens *et al.*, 1983; Ghanem *et al.*, 1987). The highest frequency and the highest levels of CICs were detected in the most severe forms and during the initial stages of the infection. Less information is available on the role, if any, of CICs in urinary schistosomiasis caused by *S. haematobium* (Cauda *et al.*, 1981; D'Amelio *et al.*, 1981; Laghi *et al.*, 1982; Stevens *et al.*, 1983).

The aim of the present study was to evaluate the presence and level of CIC in patients with chronic *S. haematobium* infection and to correlate these parameters with the clinical and parasitological findings and the urographic pictures.

Patients and Methods

A group of 69 patients was studied (51 males and 18 females, aged 34–44 years); they were inhabitants of Merere, a village in the Afgoi district, Democratic Repubic of Somalia, and were infected with *S. haematobium*. The cases were documented by the patients' history of exposure, the characteristic symptoms and the presence of *S. haematobium* in the urine. The patients were observed from 3 months to 2 years after exposure and all underwent urography. The urinary egg concentration was calculated as the mean of the values obtained in 3 different determinations, performed on non-consecutive days at 11 a.m. All patients were arbitrarily divided into 2 groups according to the mean egg count/10 ml of urine on 3 different occasions. Group 1 comprised 23 patients with less than 25 eggs/10 ml of urine and group 2 included 46 patients with more than 25 eggs/10 ml of urine. The patients

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in group 2 were younger, and had a shorter history of disease.

The sera were separated by centrifugation and stored at −20°C before shipment to Italy in dry ice. The storage of sera was no longer than 3 months.

Circulating immune complexes were measured by the polyethylene glycol (PEG) precipitation test as described by Chia *et al.* (1979). The serum level of CIC was expressed as a percentage of PEG precipitable IgG in comparison to serum IgG. A value $\geqslant 4\%$ of PEG precipitable IgG (*i.e.* mean obtained in 20 normal controls ±2 SD) was considered positive for the presence of CIC.

Twenty normal Somalis of high class, who had lived their entire life in the urban area of Mogadishu and who were without evidence of parasitic disease, were matched as controls by sex and age.

Statistical analysis was conducted using Student's *t* test, Pearson's correlation coefficient and chi-squared test.

Results

The main clinical symptoms were continuous haematuria in 41 patients (59%), periodic haematuria in 28 (41%), nocturia in 31 (45%) and dysuria in 36 (52%). Urographic changes in the urinary tract were found in 47 of 69 patients (68%): 8 of these patients were in group 1 and 39 in group 2. Single or multiple filling defects of the bladder were present in 23. The ureter was involved in 24 patients. In 21 this was associated with filling defects of the bladder, with hydronephrosis or with calcification of the bladder, but in 3 patients only the ureter was affected.

Elevated levels of circulating immune complexes were found in 39 of 69 patients (56%) (4.0 ± 1.1 *vs* 2.4 ± 0.6 of normal controls ($P < 0.01$)).

No statistical correlation was found between the presence and the level of CICs and any of the above symptoms.

A significant relationship was found between the presence of CICs and the *S. haematobium* egg output in the urine. CICs were present in 4 of 23 patients (17%) in group 1 (2.9 ± 0.9%) and in 35 of 46 patients (76%) in group 2 (4.5 ± 0.7) ($P < 0.01$). Plotting individual values of CIC levels and the output of eggs in each patient showed a linear regression coefficient ($r = 0.47$, $P < 0.001$) (Fig. 1).

CICs were present in 32 of 47 patients (68%) with urographic abnormalities of the urinary tract, but in only 7 of 22 patients (32%) without these

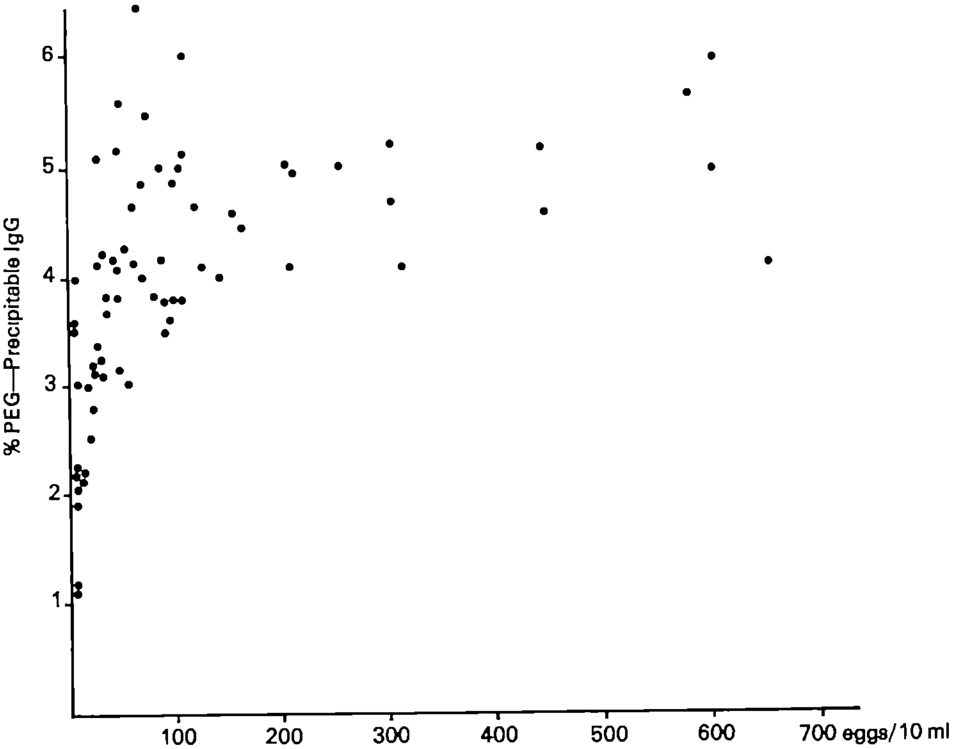

Fig. Correlation between levels of circulating immune complexes expressed as % PEG precipitable IgG and number of eggs/10 ml of urine in patients with *S haematobium*.

Table Circulating Immune Complexes in Patients with Radiological Abnormalities of the Urinary Tract

	No of patients positive for CIC (%)	*Level of CIC (% PEG precipitable IgG)*	*< 25 eggs/10 ml (CIC-positive patients)*	*> 25 eggs/10 ml (CIC-positive patients)*
Negative IVU	7/22 (32)	3.4 ± 1.0	15 (3)	7 (4)
Positive IVU	32/47 (68)	4.3 ± 0.9	8 (1)	39 (31)
Filling defects of bladder	22/23 (96)	4.7 ± 0.6	0	23 (22)
Ureteric involvement	0/3	2.3 ± 1.4	3 (0)	0
Ureteric involvement associated with filling defects of bladder and/or hydronephrosis and/or bladder calcification	10/21 (48)	4.1 ± 1.0	5 (1)	16 (9)

abnormalities (4.3 ± 0.9% and 3.4 ± 1.0% respectively) ($P < 0.01$) (Table). In particular, CICs were present in 22 of 23 patients (96%) with single or multiple defects of the bladder (4.7 ± 0.6%), in none of 3 patients with isolated ureteric involvement (2.3 ± 1.4%) and in 10 of 21 patients (48%) with ureteric involvement associated with filling defects of the bladder, hydronephrosis or bladder calcification (4.1 ± 1.0%) (Table). A positive relationship was found between the incidence of CICs and the presence of single or multiple filling defects of the bladder ($X = 19.1$, $P < 0.001$).

Discussion

The main urinary tract lesions caused by *Schistosoma haematobium* include egg granuloma of the bladder and ureters (seen as single or multiple filling defects on radiographs), hydro-ureter and hydronephrosis, calcification of the bladder and ureters, and radiographic non-function of the kidney. A correlation between these lesions and the host immune response, although suggested, has not been clearly established. In particular, the role of CICs has been the subject of increasing interest in recent years. They are thought to be responsible for immunological lesions of the kidney (Houba *et al.*, 1977) and to contribute to specific host defence mechanisms, as reported in experimental schistosomiasis (Capron *et al.*, 1977; Joseph *et al.*, 1978). Our findings show that CICs are present at a higher rate and a higher level in patients who excrete large numbers of *Schistosoma* eggs in the urine, and are associated with the presence of radiological abnormalities of the urinary tract (particularly filling defects of the bladder). Patients in whom only the ureter is involved or in whom both ureter and bladder are involved, excrete fewer eggs and have lower CIC levels. These results suggests that CICs are present in the earlier phase of chronic infection and not in the advanced stages, when ureteric involvement, hydronephrosis and bladder calcification are the most prevalent radiological findings.

The direct correlation between the level of CICs and the *S. haematobium* egg count in the urine is also indicative of more active disease in patients with CICs and is in accordance with a previous report by Santoro *et al.* (1980), which showed a similar incidence in patients with *S. mansoni* schistosomiasis. Our results, however, contrast with those of Ghanem *et al.* (1987), where no correlation was seen between CIC levels and the intensity of infections in patients with *S. mansoni* schistosomiasis. This discrepancy may be due to the different type of assay employed for measuring CICs. The positive correlation between the presence of CICs, the elimination of larger numbers of *Schistosoma* eggs in the urine and the radiological picture of filling defects of the bladder, suggests a possible pathogenic role for CICs in the early phase of the infection, when the prevalent lesion is the egg granuloma. The level of CICs declines in the advanced phases of schistosomiasis, when ureteric involvement (either alone or in association with the bladder) is the most common lesion.

CIC may play different roles, *e.g.* be deposited in the tissues and interfere with cellular functions of the immune system, such as the lymphocyte proliferative response (Colley *et al.*, 1977; Cottrell *et al.*, 1980) and eosinophil mediated cytotoxicity of parasite targets.

In both experimental and in human schistosomiasis, suppression of cellular immune mechanisms by factors of the patient's own serum has been described (Colley *et al.*, 1977; Cottrell *et al.*, 1980; Ottesen and Pointedexter, 1980). Although the nature of these suppressor factors has not yet been established, CICs may be involved.

Recent studies have demonstrated IgG, IgM and IgE isotype (Digeon *et al.*, 1979; Cottrell *et al.*,

1980) within the immune complexes in schistosomiasis. The presence of parasite products inside or outside the vascular compartment may be an important source of soluble antigen which is recognised by the specific circulating antibodies. The presence in the serum of patients with schistosomiasis of both soluble parasite antigens and specific antibodies suggests that CICs contain specific antigens (Santoro *et al.*, 1981), but there is no direct proof of this. In a previous report we demonstrated the presence of parasite-related antigens associated with circulating immune complexes in some patients affected by urinary schistosomiasis, using an ELISA assay (Manca *et al.*, 1988).

This experimental finding, together with the differences in CIC levels in patients according to the output of *S. haematobium* eggs and the presence of radiological abnormalities (including filling defects of the bladder), also suggest a pathogenic role for CICs in the chronic phase of human schistosomiasis. A better understanding can be obtained only by systematic monitoring in parallel of total CICs and specific complexes. It is suggested that early CICs contain the specific antigen and antibody, whereas later CICs contain antibodies and anti-idiotypic antibodies and/or rheumatoid factors. These changes in the composition of CICs may be the serological expression of the regulation of the specific response.

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Failure of Allopurinol to Modify Urinary Composition in Enteric Hyperoxaluria

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Summary—Conventional treatment of enteric hyperoxaluria (EHO) consists of dietary restriction of oxalate and fat and correction of its underlying cause whenever possible. Recent work suggests that allopurinol reduces the incidence of urolithiasis and the urinary excretion of both oxalate and uric acid in patients without intestinal disease. We have assessed the effect of allopurinol, 300 mg daily for 2 weeks, on urine biochemistry in patients with EHO due to small bowel Crohn's disease and/or resections. Compliance with treatment was confirmed by a fall in plasma uric acid in every patient. Allopurinol failed to alter 24 h urinary oxalate excretion or oxalate concentration. There were also no significant changes in the urinary excretion of glycollate (like oxalate, a breakdown product of glyoxylate), citrate, magnesium or calcium, each of which was at the lower end of the normal range before and during treatment with allopurinol. It appears unlikely that allopurinol will prove useful in the prevention of urolithiasis in patients with EHO.

Patients with gut disorders characterised by malabsorption of fat and/or bile acids excrete oxalate in the urine and are at increased risk of oxalate urolithiasis (Earnest, 1979; Laker, 1983; Rampton and Sarner, 1988). Enteric hyperoxaluria appears to result mainly from hyperabsorption of dietary oxalate and, apart from elimination of the underlying cause where possible, its treatment to date has depended largely on dietary measures (Earnest, 1979; Laker, 1983; Rampton and Sarner, 1988); however, the compliance of patients with advice to restrict oral intake of oxalate and fat is often poor.

Recent studies have suggested that the xanthine oxidase inhibitor, allopurinol, reduces the frequency of urinary stone-forming incidents in patients with recurrent calcium oxalate calculi unassociated with bowel disease (Coe, 1978; Lancet, 1987). This effect is accompanied by a decrease in the urinary excretion of oxalate and uric acid (Scott *et al.*, 1978; Simmonds *et al.*, 1981; Tomlinson *et al.*, 1985).

The aim of the present investigation was to assess the effect of allopurinol, given orally for 2 weeks, on the urinary composition of patients with EHO taking their normal diets.

Patients and Methods

The study group comprised 8 out-patients (6 male, 2 female, aged between 22 and 68 years) with diarrhoea and/or steatorrhoea due to small intestinal Crohn's disease and/or resection (Table 1): 3 patients had undergone a right hemicolectomy but none had overt residual colonic disease. Renal function was normal in all patients.

The protocol is summarised in Table 2. Patients were asked to remain on their customary diet throughout the study. On days 1 to 3, when the pretreatment 24-h urine collection was made, they recorded on a diet sheet exactly what they ate and drank, with particular reference to materials of high oxalate or ascorbate content (spinach, parsley, beetroot, rhubarb, peanuts, chocolate, fruit juice, cola drinks, beer, tea, coffee and ascorbic acid tablets). On days 17 to 19, when the 24-h urine specimen after 2 weeks' treatment with allopurinol (300 mg daily) was collected, they consumed exactly what they had recorded as their oral intake on days 1 to 3; dietary intake on days 17 to 19 was again

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Table 1 Details of Patients

Patient no	*Diagnosis*	*Faecal weight (g/d)**	*Faecal fat (mmol/d)†*
1	Crohn's disease of terminal ileum	300	2
2	Crohn's disease of terminal ileum	352	16
3	Ileal resection for, and later recurrence of Crohn's disease	423	19
4	Right hemicolectomy for Crohn's disease	367	26
5	Right hemicolectomy for caecal carcinoma, later small bowel Crohn's disease	369	27
6	3 small bowel resections for Crohn's disease	797	66
7	Right hemicolectomy and later further ileal resection for Crohn's disease	430	115
8	3 small bowel resections for volvulus	1467	214

* Normal <200 g/d.
† Normal <18 mmol/d.

Table 2 Protocol

Day	*Diet**	*Venepuncture*	*24-h urine collection*	*3-day faecal collection*	*Allopurinol 300 mg/d*
1	Recorded on diary card	—	—	Yes	—
2		—	—	Yes	—
3		—	Yes	Yes	—
4	—	Yes	—	—	—
5–16	—	—	—	—	Yes
17	Exactly as on days 1–3	—	—	—	Yes
18		—	—	—	Yes
19		—	Yes	—	Yes
20	—	Yes	—	—	Yes

* See text.

detailed on a diet sheet and was used to check adherence to the instructions.

All patients gave informed consent for the investigation, approval for which was granted by the Ethical Committees of Newham and City and Hackney Health Authorities.

Urinary oxalate was measured by the continuous-flow enzymatic method of Kasidas and Rose (1985). Urinary glycollate and citrate were assayed by enzymatic methods as previously described (Kasidas and Rose, 1979) and slightly modified (Moellering and Gruber, 1966); standard techniques were used to measure urinary creatinine, calcium and magnesium concentration, plasma uric acid concentration (with a uricase method) and faecal fat excretion.

Results are expressed as mean ±1 SD and were compared using Wilcoxon's signed ranks test for matched pairs and sum of ranks test for unmatched samples. Spearman's rank correlation test was used to evaluate possible correlations.

Results

Untreated patients. The urinary composition of the 8 patients is shown in Table 3.

Urinary oxalate excretion was 0.29 ± 0.16 mmol/24 h and concentration 0.23 ± 0.17 mmol/l. The urinary excretion of glycollate was within the normal range (0.10–0.33 mmol/24 h) but the output of calcium and magnesium was at the lower end of the range of values found in control subjects (2.0–9.0 and 2.0–8.0 mmol/24 h respectively). Urinary citrate was low in comparison with previously quoted normal values (Rudman *et al.*, 1980).

Urinary 24-h output of oxalate tended to vary directly (Spearman's rank correlation coefficient, $R = 0.57$) and of citrate inversely ($R = -0.57$) with faecal fat excretion, but in this small group of patients neither relationship reached statistical significance ($P < 0.1$). Urinary calcium and magnesium excretion also failed to correlate significantly with the degree of steatorrhoea.

Table 3 Urine Composition before and after Treatment with Allopurinol 300 mg daily for 2 Weeks

Variable	*Units*	*Before allopurinol*	*After allopurinol*	*P*
Volume	ml	1390±381	1376±433	NS
Oxalate output	mmol/24 h	0.29±0.16	0.32±0.26	NS
Oxalate concentration	mmol/l	0.23±0.17	0.26±0.21	NS
Creatinine output	mmol/24 h	9.6±3.8	8.9±2.4	NS
Glycollate output	mmol/24 h	0.18±0.02	0.19±0.04	NS
Citrate output	mmol/24 h	1.16±0.82	0.88±0.53	NS
Calcium output	mmol/24 h	2.2±1.7	1.6±1.3	NS
Magnesium output	mmol/24 h	2.2±1.3	1.9±1.2	NS

Results are shown as mean ± 1 SD NS denotes not significant

Effects of allopurinol. After 2 weeks' treatment with allopurinol, plasma uric acid concentration had fallen in every patient (0.30±0.11 mmol/l before treatment, 0.19±0.06 after, $P<0.05$), confirming their compliance with the medication. Mean urinary creatinine output, measured to ensure completeness of collection of the 24-h urine samples, was similar before and after treatment (Table 3).

Allopurinol did not affect urinary oxalate excretion, whether expressed as output/24 h or concentration; urinary excretion of glycollate, citrate, calcium and magnesium was also unaltered (Table 3). Patient no. 7 (Table 1) developed a transient urticarial rash after 13 days but no other side effects were observed.

Discussion

Since the urinary excretion of oxalate in patients with intestinal malabsorption depends upon its oral intake (Earnest, 1979; Laker, 1983; Rampton and Sarner, 1988), a quantitative definition of hyperoxaluria in such subjects is not possible unless the diet is standardised. For the pre-treatment phase of this investigation (days 1–3) the patients were instructed to select their usual diet, and comparison of their urinary oxalate output with a conventional "normal" range was therefore inappropriate. However, indirect evidence that these individuals were indeed hyperoxaluric came from their clinical diagnoses and levels of diarrhoea and steatorrhoea (Table 1). Further support for this conclusion was provided by comparison with results reported previously (Rampton *et al.*, 1979). The mean urinary oxalate excretion (0.29±0.16 mmol/24 h) of the present 8 patients was twice that of controls who were avoiding excess dietary oxalate in the earlier study (0.14±0.03 mmol/24 h, $P<0.01$) (Rampton *et al.*, 1979) and closely resembled that of another group of patients with EHO on a similar diet (0.25±0.14 mmol/24 h) (Rampton *et al.*, 1979).

Previous studies in patients without gut disorders suggested that allopurinol, by decreasing urinary oxalate as well as uric acid excretion, reduced urinary oxalate stone-forming incidents (Coe, 1978; Scott *et al.*, 1978; Simmonds *et al.*, 1981; Tomlinson *et al.*, 1985; Lancet, 1987). We therefore assessed the potential value of allopurinol in patients with EHO, in whom urolithiasis can be a substantial problem (Earnest, 1979; Laker, 1983; Rampton and Sarner, 1988). In the event, no significant changes in urinary oxalate excretion were detectable after 2 weeks' treatment. The mechanism whereby allopurinol, given for the same duration (Tomlinson *et al.*, 1985), reduces urinary oxalate excretion in patients with overtly normal intestinal function is not yet clear. Why it fails to do so in patients with EHO is equally obscure but is presumably related to the different mechanisms of hyperoxaluria pertaining in the latter. The lack of change in urinary glycollate excretion found here suggests that allopurinol did not markedly influence production of glyoxylate, the metabolism of which appears to be normal in patients with EHO (Earnest, 1979; Laker, 1983; Rampton and Sarner, 1988).

Factors other than its oxalate content contribute to the lithogenicity of the urine of patients with intestinal malabsorption (Smith, 1980). We have confirmed earlier reports that patients with gut disorders tend towards hypomagnesuria (Booth *et al.*, 1963; Rudman *et al.*, 1980). Since urinary citrate levels vary with gender and pH (Fraser *et al.*, 1985), this variable has no universally applicable normal range. Nevertheless, the values obtained here (1.16±0.82 mmol/24 h) were substantially lower than those quoted for a group of normal subjects of both sexes by Rudman *et al.*

(1980) (3.51 ± 0.22 mmol/24 h); furthermore, they were only slightly higher than the values these authors reported for patients with steatorrhoea due to jejuno-ileal bypass (0.56 ± 0.11 mmol/24 h). Excretion of neither magnesium nor citrate was affected by treatment with allopurinol in the present study.

The hypocalcuria observed here and previously, although not invariably (Gregory *et al.*, 1977, Rudman *et al.*, 1980), may be one of the factors militating against calculus formation in steatorrhoeic patients: again it failed to alter significantly after allopurinol.

In conclusion, the results of this 2-week trial make unlikely a therapeutically useful role for allopurinol in the prevention of urolithiasis in patients hyperoxaluric because of bowel disease or resection.

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Inhibitory Effect of Pyrophosphate, Citrate, Magnesium and Chondroitin Sulphate in Calcium Oxalate Urolithiasis

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Summary—The inhibitory capacity of pyrophosphate, citrate, magnesium and chondroitin sulphate was investigated, using the urine of 21 calcium oxalate stone-forming patients without metabolic alterations. The inhibitory effect of these substances was assessed by a combination of nephelometry (light scattering) and optical microscopy. The results showed that citrate and magnesium had an inhibitory effect in a significant number of cases. Pyrophosphate and chondroitin sulphate had a less marked effect. The main urinary lithogenic biochemical parameters of the patients were also studied to see if there was a relationship between them and the inhibitory capacity of the compounds.

Urolithiasis results from a combination of 3 main factors: those which affect nucleation (homogeneous or heterogeneous), those which are linked to crystalline growth and those which influence crystal aggregation. Formation of the calculus also implies fixation of the incipient crystal, because it must either remain trapped in the urinary tract or become attached to the renal epithelium. The inhibitory theory supports the existence of substances that prevent or retard nucleation, crystal growth and/or crystal aggregation. To demonstrate these inhibitory effects various methods have been employed (Robertson *et al.*, 1973; Phaneuf-Mimault and Tawashi, 1977; Azoury *et al.*, 1986). However, there are conflicting opinions regarding the effect of these inhibitory substances (Robertson and Peacock, 1985). We have developed a simple method to study inhibitory effects in urine based on the use of nephelometry and optical microscopy (Grases *et al.*, 1988) and it has been established that the effect on calcium oxalate crystallisation exerted by a given compound depends on the type of urine used. Thus the most effective inhibitor for each individual must be determined by using his or her own urine.

We present a report on the inhibitory capacity of several compounds (pyrophosphate, citrate, magnesium and chondroitin sulphate) using the urine of 21 stone-forming patients. We also investigated the patients' urinary lithogenic biochemical parameters to see if there was any relationship between them and the inhibitory capacity of a given compound.

Patients and Methods

Stock solutions included an aqueous solution of 5.7×10^{-2} M sodium oxalate (Merck) and 0.25 M calcium chloride (Merck). The following reagents were also used: magnesium nitrate (Merck), chondroitin sulphate (Sigma), tetra-sodium pyrophosphate (Merck) and monosodium citrate (Panreac). A Perkin-Elmer LS-5 spectrofluorimeter was used.

Measurement of inhibitory activity

The inhibitory effect of citrate, magnesium, pyrophosphate and chondroitin sulphate on calcium oxalate crystallisation was evaluated by a combination of nephelometry and optical microscopy (Grases *et al.*, 1988). Patients with infected urine, hypercalciuria and/or hyperuricosuria were excluded from the study.

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Table 1 Summary of Biochemical Data

Patient no	*Diuresis (ml)*	*Ca (mg/l)*	*Mg (mg/l)*	*Phosphorus (mg/l)*	*Oxalate (mg/l)*	*Uric acid (mg/l)*	*Citrate (mg/l)*	*Inhibitory effects*
1	1160	116.2	56.6	556	21.4	507	445	Magnesium
2	775	273.2	70.1	678	29.6	667	208	Pyrophosphate and magnesium
3	1620	94.7	70.8	442	21.1	487	541	Citrate and magnesium
4	1110	198.4	54.8	1005	20.3	591	432	Citrate
5	1860	99.4	36.4	568	12.3	449	173	Magnesium and glycosaminoglycans
6	1440	116.1	49.0	500	20.0	322	286	Citrate and magnesium
7	2590	52.7	21.2	177	10.7	320	193	Citrate
8	2270	110.5	36.9	379	11.9	328	239	Citrate and magnesium
9	1770	110.0	41.7	597	14.3	339	254	None
10	1610	79.6	39.7	631	14.8	315	421	Citrate and pyrophosphate
11	1720	100.9	53.3	508	19.6	494	212	Magnesium
12	1630	124.0	54.5	623	19.4	558	246	Citrate and magnesium
13	1000	177.8	59.7	526	27.5	828	208	Citrate and magnesium
14	1500	141.7	59.3	568	21.3	449	331	Magnesium
15	1520	121.6	56.8	833	18.5	406	123	Citrate and magnesium
16	2150	43.9	25.5	229	16.5	304	252	Citrate and magnesium
17	2370	87.0	37.2	314	13.1	215	395	None
18	1930	141.0	49.0	589	13.9	377	198	Magnesium
19	1060	80.7	46.6	560	32.8	504	305	Citrate
20	1490	160.3	46.4	499	21.1	504	425	Citrate
21	2400	80.4	47.7	348	14.9	370	279	Citrate, magnesium and pyrophosphate

Inhibitors were defined as compounds producing inhibitory effects when the α/α_0 coefficient (8) was $\leqslant 0.5$, for 500 mg/l citrate, 50 mg/l Mg(II), 30 mg/l pyrophosphate and 50 mg/l chondroitin sulphate.

Urine was collected under standard conditions in order to achieve maximum reproducibility for each individual. Thus the test urine corresponded in every case to urine accumulated over a 2-h period following an overnight fast. The samples were maintained at 37°C and analysed immediately. Before being measured, they were passed through an 0.45 μm pore filter. The study was repeated 3 times for each patient.

Results

The results are summarised in Table 1. Inhibitory activity was associated with magnesium in 14 samples, with citrate in 13, pyrophosphate in 3 and GAGS (chondroitin sulphate) in only 1. In 2 samples none of the compounds showed any inhibitory activity.

Discussion

The patients in whom citrate had a marked inhibitory effect presented with significantly less calcuria (concentration and total excretion) than did those individuals in whom citrate had very little effect (Table 2). Table 3 shows that calciuria (concentration and total excretion) was greater and citraturia (concentration and total excretion) was

Table 2 Concentration and Total Calcium Excretion in Relation to Inhibitory Effect of Citrate

	Mean values	*SD*	*SEM*
Cases where citrate had a marked effect			
Ca (mg/die)	168.6	51.0	14.1
Ca (mg/l)	110.8	46.4	12.9
Cases unaffected by citrate			
Ca (mg/die)	198.7	35.0	12.4
Ca (mg/l)	133.7	59.6	21.1‡

Significance of the differences into 2 groups: $^*P<0.05$; $\dagger P<0.01$, $\ddagger P<0.001$

Table 3 Concentration and Total Calcium and Citrate Excretion in Relation to Inhibitory Effect of Magnesium

	Mean values	*SD*	*SEM*
Cases where magnesium had a marked effect			
Ca (mg/die)	183.1	46.4	12.4
Ca (mg/l)	124.4	52.9	14.1
Citrate (mg/die)	432.5	202.9	54.2
Citrate (mg/l)	267.1	109.9	29.4
Cases unaffected by magnesium			
Ca (mg/die)	173.9	51.5	19.5
Ca (mg/l)	109.8	51.5	19.5
Citrate (mg/die)	588.9	194.5	73.5*
Citrate (mg/l)	346.1	95.9	36.2*

Significance of the differences into 2 groups: $^*P<0.05$; $\dagger P<0.01$, $\ddagger P<0.001$

significantly less in patients in whom magnesium produced a marked inhibitory effect compared with patients who were unaffected by magnesium. This can be explained by considering that these effects must be related to adsorption processes and may be affected by several factors, *e.g.* pH, ionic strength and the presence of other active substances. Since the composition of urine varies from one person to another, the factors that affect adsorption processes also vary, with resultant changes in inhibitory effects.

It was concluded that there is a relationship between the inhibitory effect of a particular compound and the routinely measured biochemical parameters. However, only when a large number of patients has been studied can any relationship be established with confidence.

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Percutaneous Nephrostomy in the Management of Malignant Ureteric Obstruction

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Summary—A study was made of 16 patients who developed renal failure secondary to ureteric obstruction by tumour. All were managed by percutaneous nephrostomy inserted under local anaesthesia. The results in terms of recovery of renal function, subsequent management and long-term outcome are described.

The development of bilateral ureteric obstruction secondary to pelvic malignancy, if left untreated, is a terminal event leading to death in a short period of time. However, the obstructed urinary tract can be decompressed with rapid restoration of renal function. This course of action has been both criticised and avoided by clinicians in the recent past because of the lack of effective treatments for the causative malignancy, with such clinicians preferring the patient to reach a terminal state as a result of renal failure rather than die of the painful, unchecked effects of advancing pelvic malignancy. With the increasing availability of chemotherapeutic agents and improved techniques of radiotherapy, drainage of the upper urinary tract may afford the necessary time for the oncologist or radiotherapist to instigate possible therapeutic regimes. In the past, the upper urinary tract was frequently drained by an open, surgical nephrostomy, but the newer techniques of percutaneous nephrostomy and ureteric stenting have made upper tract drainage much simpler, although there is no uniform agreement on which of these 2 methods is the better.

Patients and Methods

Sixteen patients were treated over an 18-month period. The types of tumour and the numbers in each group are shown in Table 1. There were 8 males and 8 females with a mean age of 64 years (range 49–84). All patients presented in established renal failure with oliguria and biochemical disturbance (Table 2). One patient with a plasma urea of 12 mmol/l was included because of rapidly rising creatinine and potassium levels. In 4 of the 16 patients renal failure constituted the initial presentation and in the remaining 12 it developed as a complication of a previously diagnosed tumour. All patients were managed by ultrasound guided percutaneous nephrostomy inserted under local anaesthesia.

Table 1 Tumour Types and Number of Patients in Each Group

Tumour type	*No of patients*
Bladder	8
Prostate	3
Cervix	2
Colorectum	2
Lymphoma	1
Total	16

Table 2 Mean Urea, Creatinine and Potassium Levels Before and One Week After Nephrostomy Insertion

	Before insertion (range)	*After insertion (range)*
Urea (mmol/l)	34.4 (12–74)	14 1 (8.9–36.5)
Creatinine (μmol/l)	966 (227–1788)	336 (133–1326)
Potassium (mmol/l)	5.0 (4.6–8.3)	4.2 (3 6–5.2)

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Results

All nephrostomies were inserted successfully on the first occasion. Table 2 shows the fall in mean urea, creatinine and potassium levels 1 week after insertion. In all but 2 patients the serum biochemistry had returned to near normal within 48 h. In these 2 patients the biochemistry improved gradually over the course of 1 week but did not return to normal levels.

One patient with colonic carcinoma underwent no further treatment and died 6 weeks after nephrostomy insertion. The second patient with colonic carcinoma was subsequently managed with a retrograde ureteric stent and survived for 13 months with no treatment of the tumour.

The remaining 14 patients all underwent radical radiotherapy to the pelvis in courses lasting from 4 to 6 weeks. In 5 patients the nephrostomy catheter was removed on completion of radiotherapy and no further treatment was required. Five patients underwent permanent urinary diversion into an ileal conduit. Two patients were managed by insertion of a retrograde ureteric stent and 1 by uretero-neocystostomy; 1 patient died 6 weeks following insertion, shortly after completion of radiotherapy, and her clinical condition precluded any attempt at definitive management.

Of the 16 patients, 10 (62%) were alive at 6 months. The patient described above, who died shortly after completion of radiotherapy, remained in hospital throughout the 6-week period. The remaining patients were able to go home and all of those who survived for 6 months were able to spend more than 2 months at home, fulfilling the definition by Grabstald and McPhee (1973) of a good quality of life.

The most frequent complication was blockage of the nephrostomy catheter; this could be managed successfully by regular flushing on an in-patient or out-patient basis. In 4 patients the blockage could not be cleared and the catheters were replaced. Urinary infection occurred in 7 patients but there were no major septic complications. Haemorrhage following insertion as described by Dudley *et al.* (1986) was not observed in this series, although mild transient blood staining of urine was common.

Discussion

For many years there has been debate about the ethics of decompressing bilateral ureteric obstruction secondary to advanced pelvic malignancy. Operative insertion of nephrostomy catheters and formal urinary diversion in the presence of renal failure carry formidable morbidity and mortality rates, with prolonged hospitalisation of patients who have a limited life expectancy. In the series reported by Holden *et al.* (1979), operative nephrostomy was wholly or partially responsible for the deaths of 34% of their patients. Kihl and Bratt (1981) reported an operative mortality rate of 18% in patients with prostatic carcinoma undergoing uretero-neocystostomy. In a series of 72 patients with malignant urinary obstruction, Chisholm and Shackman (1968) favoured upper urinary tract diversion by nephrostomy, pyelostomy or ureteric intubation to ileal conduit or uretero-colic anastomosis. The former methods produced lower morbidity and mortality than permanent diversion. More recently the use of endoscopic and percutaneous techniques has largely overcome the immediate post-operative mortality, but the long-term outcome and particularly the quality of life remain unclear.

In the present series, long-term outcome was good with 62% alive at 6 months. It is, of course, probable that survival was influenced by clinicians pre-selecting good prognosis patients and it is perhaps significant that 14 of our patients had tumours which were potentially radiosensitive. The quality of life was also good in our patients, with 62% surviving for more than 2 months out of hospital. Fears that patients would be condemned to a short life with a permanent indwelling nephrostomy were also groundless, with no patient surviving beyond 6 weeks left with a permanent nephrostomy. Five patients underwent a formal urinary diversion and the remaining 9 were able to pass urine normally. In the study by Chisholm and Shackman (1968), 55% of patients died without leaving hospital, 20% died approximately 2 months after discharge and only 25% survived more than 6 months. This study, however, included many patients whose urinary tracts were drained either by the definitive treatment for the obstruction (cystectomy, ileal conduit, ureterosigmoidostomy) or by upper tract decompression during radiotherapy. Many of these patients were also subjected to dialysis.

We feel that preliminary drainage of the obstructed urinary tract by this simple method will allow the return of reasonable kidney function and carry less mortality and morbidity. It will also allow an opportunity for fuller assessment of the patient's malignancy prior to definitive treatment.

It would perhaps have been more valid to analyse survival separately according to each individual tumour type, since some reports suggest better survival in patients with prostatic carcinoma (Chisholm and Shackman, 1968; Fallon *et al.*, 1980; Kihl and Bratt, 1981). In the present series, however, numbers were small and follow-up limited, so that this information is unlikely to have been helpful.

A further controversy surrounding this issue concerns the best method of decompression, the choice lying between retrograde ureteric stent insertion or percutaneous nephrostomy. The issue has been clouded by the inclusion in some series of patients with normal renal function and it seems obvious that the management of this group will be different from the management of patients in renal failure. Retrograde stent insertion is usually performed under general anaesthesia, which can be hazardous in patients with hyperkalaemia and fluid overload. Some authors recommend general anaesthesia only in patients with a serum potassium below 6 mmol/l (Hewitt, 1970; Slanson, 1972). This would have precluded general anaesthesia in 31% of our patients.

The success rate of retrograde stent insertion is a further disadvantage and despite reports of success in 80 to 85% of cases (Hepperlen *et al.*, 1979; Sing *et al.*, 1979), other reports quote a much lower success rate because of tumour distorting the bladder base and obscuring the ureteric orifices (Khan and Utz, 1975). This compares with our success rate of 100% and is an important factor in patients with compromised renal function, particularly those with hyperkalaemia, where renal tract decompression is a matter of urgency.

In conclusion, we agree with Dudley *et al.* (1986) and recommend percutaneous nephrostomy because of the ease and simplicity of insertion in a life-threatening situation. This allows the patient's renal function to recover and definitive treatment may then be planned. Obviously, percutaneous nephrostomy does not preclude the subsequent use of indwelling ureteric stents inserted in either an antegrade or retrograde fashion.

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Beta Human Chorionic Gonadotrophin in Serum and Urine. A Marker for Metastatic Urothelial Cancer

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Summary—Beta human chorionic gonadotrophin (βHCG) was measured in 127 urine and 85 serum samples from 175 untreated patients with urothelial cancer. Serum levels of βHCG were substantially elevated in 16 of 21 patients (76%) with widespread metastases but in only 2 of 64 patients (3%) with disease confined to the pelvis. Urine βHCG levels were moderately raised in 11 of 25 patients (44%) with locally advanced disease, but greatly elevated in 5 of 7 patients (71%) with metastases. Measurement of serum and/or urine βHCG appears to be an efficient diagnostic marker for the presence of distant metastases in bladder carcinoma.

Secretion of human chorionic gonadotrophin (HCG) by germ cell tumours is well recognised (Braunstein *et al.*, 1981; Braunstein, 1983). HCG production by urothelial tumours was first described by Civantos and Rywlin (1972) and there have been sporadic reports since then (Kawamura *et al.*, 1978; Fukutani *et al.*, 1983; Obe *et al.*, 1983; Gallagher *et al.*, 1984; Rodenburg *et al.*, 1985). In blood, the principal form of HCG is a molecule similar to the free beta subunit (Hattori *et al.*, 1980; Rodenburg *et al.*, 1985; Norman *et al.*, 1986). *In vitro*, both neoplastic and "normal" urothelial cell lines are known to secrete an HCG-like molecule into culture media (Iles *et al.*, 1987). We examined βHCG levels in the serum and urine of patients with bladder cancer and demonstrated a strong association between elevated levels of HCG and metastatic disease.

Patients and Methods

The study group comprised 175 patients with bladder cancer. Early morning urine specimens (EMU) were collected from 127 patients (Table). A blood sample was collected on the same day from 35 of these and in a further 48 cases a blood sample only was collected.

The grade and stage of tumours were defined according to the UICC (1978) system. All samples were obtained before treatment by surgery or chemotherapy. Control EMUs were collected from 23 age-matched in-patients on the orthopaedic wards. The mean age of the patients was 67 years (range 39–91) and of controls was 68 years (range 54–86). Samples were assayed for βHCG by radioimmunoassay (RIA), using a polyclonal anti βHCG antibody S424 (ILS Ltd, UK) (Norman *et al.*, 1986). This assay recognises both the free beta subunit and the intact hormone. The detection limit is 25 iu/l.

Results

The relationship between serum βHCG and disease stage is shown in Figure 1. No stage T0 (clear on cystoscopy) patient had a detectable level of HCG

Table Numbers of Samples and Patients in each Category of Bladder Carcinoma

	Stage of disease				
	T0	*TA/1*	*T2/3*	*T4*	*N+/M+*
No. of patients	43	62	30	19	21
No. of serum samples	9	23	18	14	21
No. of urine samples	39	56	17	8	7

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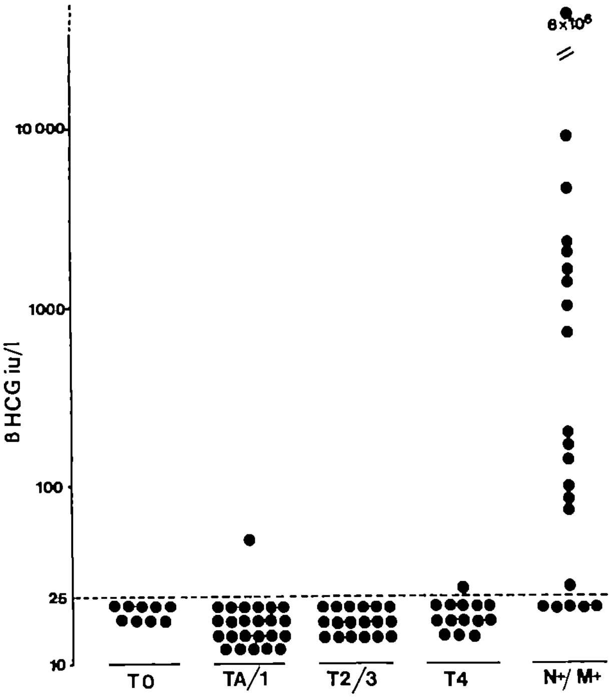

Fig. 1 Serum levels of βHCG in patients with various stages of bladder cancer

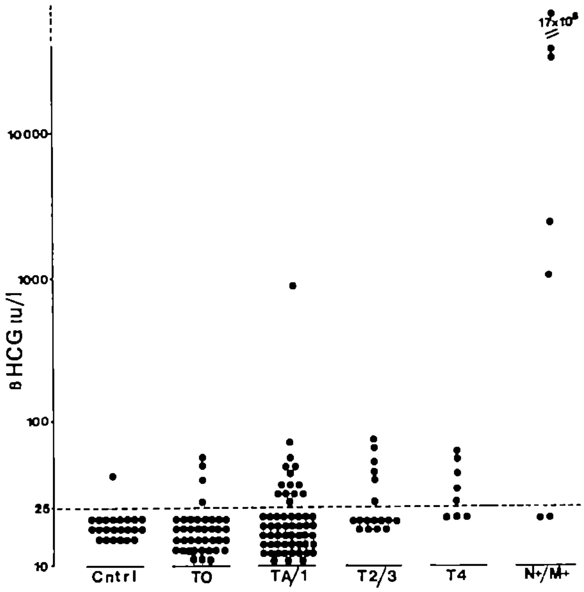

Fig. 2 Urine levels of βHCG in EMU samples from age-matched controls and patients with various stages of bladder cancer

in serum. In the local to advanced invasive (Ta–T4) categories, 2 of 55 patients (4%) had detectable levels (26 and 50 iu/l). Sixteen of the 21 patients with widespread metastatic disease (76%) had elevated serum levels of βHCG (median 160 iu/l; range 28–6 million).

Urinary βHCG levels for the various disease stages are shown in Figure 2. One of the 23 controls (4%) and 4 of 39 T0 patients (10%) had detectable βHCG levels, compared with 14 of 57 patients with local Ta/1 disease (25%) and 11 of 25 patients with invasive to advanced invasive disease (T2–T4) (44%). In these categories, urine βHCG exceeded 70 iu/l in only 1 case (900 iu/l); 5 of 7 patients (71%) with metastatic disease had an elevated urinary βHCG (median 1660 iu/l; range 1060–17 million).

Paired urine and blood samples were available for 35 patients. Only those patients with metastases had levels >25 iu/l in both samples. In these cases the urinary βHCG levels (median 18,150) were greater than those in serum (median 2975).

Discussion

A review of elevated circulating HCG levels in patients with non-germ cell malignant disease gave an incidence of 18% among 7127 patients (Braunstein, 1983). For specific tumours, the incidence ranged from 4% (leukaemia–lymphoma) to 45% (islet cell carcinoma). Only 10% of patients with bladder cancer were reported to be positive. However, Dexeus *et al.* (1986) found detectable serum levels of βHCG in 28 of 92 patients (30%) with "advanced urothelial tumours".

Immunohistochemical studies suggest that HCG is commonly expressed by many different tumours (McManus *et al.*, 1976; Bellett *et al.*, 1980). The incidence of HCG synthesis by bladder tumours, as measured by immunohistochemical techniques, has been variously estimated at 5 of 13 cases (Rodenburg *et al.*, 1985) and 12 of 104 cases (Shah *et al.*, 1986). In these studies most of the positive tumours were poorly differentiated and at an advanced stage.

In the present study, the tumours were staged clinically. The presence of metastases was assessed by CT scanning and/or chest X-ray, which may underestimate the extent of metastases as a much higher incidence is found in autopsy studies. Kishi *et al.* (1981) found metastatic deposits in 2 of 11 patients (18%) with supposedly local disease (TA/1) and in all 12 patients in whom invasion had progressed beyond the bladder (T4). In a study of patients subjected to cystectomy, Smith and Whitmore (1981) reported local lymph node metastases in 2 of 37 T1 patients (5%) and 47 of 106 T4 patients

(44%). The most common metastatic sites were the lymph nodes (38%), followed by the lungs (30%), liver (30%) and bone (24.1%). Of the lymph node deposits, 52% were within the renal pelvis, 25% abdominal and 34% thoracic (Kishi *et al.*, 1981).

In this study, βHCG was detected in the serum of 76% of patients with clinically detectable metastases, in contrast to only 4% of those with disease limited to the pelvis and without clinical evidence of metastases. Only patients with widespread metastases had levels of HCG exceeding 100 iu/l in the urine; those with locally invasive disease showed occasional positive values which did not exceed 100 iu/l. Patients with advanced invasive (T4) disease, who almost certainly would have some microscopic metastatic deposits in local lymph nodes, did not have elevated serum levels of HCG or grossly elevated levels in the urine.

The variation in βHCG secretion with disease stage might simply be due to differences in the total mass of tumour. However, if bulk were the sole factor, the discrepancy between advanced invasive and metastatic disease should be considerably less. It is therefore possible that secretion of βHCG might characterise a more aggressive tumour.

HCG secretion by bladder cancer is now recognised as being a more common phenomenon than previously believed (Burry *et al.*, 1986; Shah *et al.*, 1986, 1987). Measurement of serum levels may also be of clinical value in monitoring the response to chemotherapy (Dexeus *et al.*, 1986). We have shown that HCG estimation has practical value as an effective marker of widespread metastatic bladder cancer. Thus the finding of elevated serum levels of βHCG (>25 iu/l) has a predictive value of 89%, a specificity of 96% and a sensitivity of 76%; elevated urine levels (>100 iu/l) have a predictive value of 83%, a specificity of 99% and a sensitivity of 71%.

Of particular interest are those patients with elevated levels of HCG but without clinical signs of distant metastases. They are the subject of close follow-up to discover if they subsequently develop widespread disease. If immunohistochemical and urinary HCG can be used as a marker of aggressive tumours, it may be of considerable clinical importance in the selection of patients with poor prognosis who would be suitable for an alternative form of treatment (Jenkins *et al.*, 1988).

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Flow Cytometry Analysis of Leucocytes Infiltrating Bladder Tumours According to Grade and Urothelial Cell DNA Content

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Summary—A series of 76 bladder tumours was studied using a panel of 5 anti-human leucocyte monoclonal antibodies (mAb): anti-pan-leucocytes (SLC1), anti-T lymphocytes (ST1), anti-B lymphocytes (SB3), anti-macrophages (PHM2) and anti-granulocytes (WEMG1). The DNA content and the expression for each mAb were measured in separate samples with flow cytometry. The importance of local inflammatory reaction was measured objectively according to tumour grade. These cells formed 41, 32 and 31% of the total cell count for grade I, II and III tumours respectively. The percentage of each leucocyte population according to grade I, II or III was as follows: 8, 5 and 6% respectively for T-lymphocytes; 3, 3 and 4% for B-lymphocytes; 10, 7 and 6% for granulocytes; 17, 18 and 24% for macrophages. No relationship was found between mAb expression and DNA content of tumours. This study demonstrates the importance of the inflammatory reaction in bladder tumours and the preponderance of cells expressing a macrophage phenotype. In a flow cytometry study, leucocytes may mask the presence of a minor group of urothelial tumour cells with an elevated DNA content associated with a poor prognosis; on the other hand, host leucocytes within a tumour could be used as an internal reference for precise measurement of the DNA content of tumour cells.

Since the first report of a successful attempt to reduce the recurrence of superficial bladder tumours by intravesical administration of BCG (Morales *et al.*, 1976), several studies have suggested that stimulation of a local inflammatory response (Lamm *et al.*, 1982) and induction of interleukin-2 synthesis by T-cells (Haaff *et al.*, 1986) may contribute to the efficacy of the treatment (Droller, 1986). A few studies have been devoted to the immunohistochemical characterisation of leucocyte populations which infiltrate normal urothelium (El Demiry *et al.*, 1986) and bladder tumours treated with BCG (El Demiry *et al.*, 1987). However, immunohistochemical techniques do not permit a precise quantification of each cell type in the leucocyte infiltrate, and possible quantitative as well as qualitative alterations of infiltrating cells according to tumour grade remain a point for discussion.

We have reported on the measurement of cell DNA content of bladder tumours and demonstrated that a bimodal DNA profile was linked to tumour aggressiveness and poor prognosis (Devonec *et al.*, 1986). In the present study we determined the percentage of cells that expressed antigens associated with all leucocytes (T-cells, B-cells, monocytes/macrophages and polymorphonuclear neutrophils) by indirect immunofluorescence and flow cytometry. The data were obtained from 76 bladder tumours and analysed according to tumour grade and cell DNA content.

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Patients and Methods

Biopsies were taken from 76 patients who presented with either a primary or recurrent bladder tumour previously treated by transurethral resection only. Among these 76 tumours there were 11 grade I, 33 grade II and 32 grade III (World Health Organisation classification). The 11 grade I tumours were non-infiltrating stage pTa; of the 33 grade II tumours, 24 were stage pTa and 9 were stage pT1. Of the 28 grade III tumours, 8 were pTa, 3 were pT1 and 17 were pT2 or a higher stage. The last 4 tumours were *in situ* carcinomas.

Frozen tumour fragments were thawed and mechanically dissociated on a mesh in phosphate buffered saline containing PBS-EDTA (140 mM NaCl, 8 mM Na2HPO4-2H2O, 1.67 mM NaH2PO4-H2O, 1 mM EDTA, pH 7.2). The cell suspension was filtered and then centrifuged at 250 × g for 15 min; the pellet was washed once in PBS-EDTA. Cells were suspended in 0.5 ml buffer and adjusted to 2×10^6 cells/ml.

The main characteristics of the monoclonal antibodies used for cell surface immunofluorescence are shown in Table 1. SLC1, SB3 and ST1 were provided by Sanofi Research Center (Montpellier, France). Antibodies PHM2 and WEMG1 were purchased from Eurobio (Paris, France). All of these antibodies were used at the final optimal concentration of 10 μg/ml, in flow cytometry. The second antibody was a fluorescein isothiocyanate conjugated FITC-F(ab')2 fragment of a goat anti-mouse immunoglobulin (Eurobio, Paris, France) used at 1/50 dilution.

Urothelial cells were incubated with the mAbs for 60 min at +4°C, then washed twice at 250 × g in PBS-bovine serum albumin (BSA) buffer (140 mM NaCl, 8 mM Na2HPO4-2H2O, 1.67 mM NaH2PO4-H2O, 2% BSA, pH 7.2). The pellet was then resuspended in the FITC-F(ab') 2 solution, in the dark, for 30 min at +4°C. Following 2 washes, cells were then fixed in 4 ml total volume of a freshly prepared 1% paraformaldehyde solution for 30 min at room temperature. Cells were further washed and resuspended in 100 μl PBS-EDTA buffer. DNA staining was performed on a separate sample according to the method described by Vindelov (1977) using a 50 μl/ml propidium iodide solution.

Cell suspensions labelled with mAbs, or stained for DNA were examined with an Ortho 50H cytofluorograph (Ortho-instruments). Cells were exposed to a 488 nm argon ion laser irradiation. Surface and peak of the green or red fluorescence were recorded from 5000 cells/sample. For each tumour 2 control cell suspensions were systematically used. The first control contained chicken erythrocytes as internal standard for the calculation of DNA index according to our previous studies (Devonec *et al.*, 1986; Hijazi *et al.*, 1987). The second control contained the FITC anti-mouse IgF(ab') 2 antibody without mAb. It permitted the definition of the threshold of fluorescence intensity above which cells were considered to be positive. Fluorescence intensity was displayed on an arithmetic linear scale and expressed in arbitrary units. The numbers of cells labelled by each mAb and mean fluorescence intensities were compared by using the F variance analysis test.

Results

DNA Content

Analysis of histograms of DNA content for each tumour revealed 2 groups. The first group of 38 tumours was characterised by a unimodal DNA profile showing a single peak with a DNA index of 1.00 ± 0.02. In the second group of 38 tumours, the DNA profile was bimodal, showing a first peak with a DNA index of 100 ± 0.02 and a second peak with a DNA index of 1.85 ± 0.22 (extremes 1.56 and 2.20).

In agreement with our previous series (Devonec *et al.*, 1986), the proportion of tumours with a bimodal DNA profile increased in parallel with tumour grade. All grade I tumours, 23 grade II and only 4 grade III tumours were unimodal. A bimodal

Table 1 Characteristics of Anti-leucocyte Monoclonal Antibodies

mAbs	*Class*	*Antigen*	*Cluster*	*Target cells*	*Reference*
SLC1	IgG1	T200, LCA	CD45	Pan-leucocyte	Battifora and Trowbridge (1983)
SB3	IgG1	Gp 40–45	CD37	Mature B-cells (T-cells)	McMichael (1987)
ST1	IgG2a	p67	CD5	Mature T-cells (B-CLL)	McMichael (1987)
PHM2	IgG1	S2K	*	Macrophages (5% T)	Becker *et al* (1981)
WEMG1	IgM	110K	*	Granulocytes	Lopez and Vadas (1984)

*Unidentified.

DNA profile was encountered in 10 of 33 grade II tumours and 28 of 32 grade III tumours (Table 2).

Percentage of cells recognised by monoclonal antibodies

The mAb SLC1 (anti-CD45) labelled an average of 41% cells in grade I tumours and significantly less ($P<0.01$, *t* test) in grade II and III tumours (Table 2). A few T cells and granulocytes identified respectively by Mabs ST1 (anti-CD5) and WEGM1 were found in grade I tumours. The percentages were slightly lower in grade II or III tumours, although the differences did not reach statistical significance. Very few CD37 positive B cells were found, whatever the grade. Cells identified by PHM2 mAb accounted for about 17% of the whole cell population of grade I and II tumours, but this percentage was significantly increased in grade III tumours ($P<0.001$, *t* test).

An analysis was then performed separately on unimodal and bimodal tumours (grades II and III). No difference in the percentage of cells labelled with anti-CD45 (pan-leucocytes), anti-CD5 (T-lymphocytes), anti-CD37 (B-lymphocytes) and by WEMG1 (granulocytes) was found between unimodal and bimodal tumours. However, the percentage of cells bearing the epitope recognised by the PHM2 mAb (monocytes/macrophages) was markedly greater in bimodal than in unimodal tumours (Table 2). Furthermore, the percentage of cells labelled by the anti-CD45 mAb in grades I, II or III was approximately the sum of that recognised by each of the other mAbs in the corresponding grade, with the exception of bimodal tumours. Since the number of cells labelled with PHM2 mAb, but not by other mAbs, was greater in the bimodal group, it was assumed that in this group some cells were both CD45 negative and PHM2 positive, *i.e.* were not leucocytes but expressed the monocyte/macrophage phenotype.

The mean fluorescence intensities of cells labelled by each of the monoclonal antibodies are presented in Table 3. The values were comparable to those obtained with the same mAbs on peripheral blood leucocytes (data not shown). Mean fluorescence intensities did vary according to mAbs but were rather similar for one mAb according to tumour grade or to DNA profile.

Discussion

In this study, leucocytes infiltrating bladder tumours were identified by monoclonal antibodies and quantified by flow cytometry. This method differs in principle from immunohistochemical characterisation of tissue sections performed in other studies (El Demiry *et al.*, 1986, 1987). It does not permit the assessment of the distribution of infiltrating cells or their topographical relationship with tumour cells. Conversely, flow cytometry allows a precise quantification of the percentage of labelled cells and the analysis of changes in the composition of the cell infiltrate according to the DNA profile of each tumour.

The present data are in agreement with other studies showing the presence of T-cells and macrophages in the stromal reaction of bladder tumour cells (Hanai *et al.*, 1985; Gardiner *et al.*, 1986). Various proportions of CD4+ and CD8+ T-cells have been reported in bladder tumour infiltrate as well as a few B-lymphocytes (El Demiry *et al.*, 1987). The main findings in the present study were the significant proportion of polymorphonuclear leucocytes, which represent about 25% of the

Table 2 Percentage of Cells* Reacting with Anti-leucocyte Monoclonal Antibodies according to DNA Content and Tumour Grade

			Percentage of cells reacting with				
Tumour	*DNA profile*	*N*	*LCA SLC1*	*Macrophage PHM2*	*Grans WEMG1*	*T ST1*	*B SB3*
Grade I	Unimodal	11	41±4	17±4	10±2	8±3	3±1
Grade II	Total	33	32±8	18±5	7±3	5±1	4±2
	Unimodal	23	34±8	17±5	7±2	5±1	3±1
	Bimodal	10	29±6	21±5	8±2	5±1	6±2
Grade III	Total	32	31±4	24±5	6±1	6±2	4±2
	Unimodal	4	34±3	20±5	6±2	6±2	2±1
	Bimodal	28	31±4	25±5	6±1	6±2	4±2

*Mean ± SD

Table 3 Mean fluorescence Intensity of Cells* labelled with Anti-leucocyte Monoclonal Antibodies according to DNA Profile and Tumour Grade

			Mean fluorescence intensity				
Tumour	*DNA profile*	*N*	*LCA SLC1*	*Macrophage PHM2*	*Grans WEMG1*	*T ST1*	*B SB3*
Grade I	Unimodal	11	62±17	78±28	80±15	103±16	96±22
Grade II	Total	33	59±15	84±31	88±20	89±24	105±26
	Unimodal	23	65±14	90±29	85±22	100±23	106±17
	Bimodal	10	69±16	83±23	82±20	96±21	103±23
Grade III	Total	32	62±7	79±18	87±17	96±20	99±9
	Unimodal	4	65±13	86±19	91±18	101±26	105±17
	Bimodal	28	63±14	82±15	93±12	102±22	99±19

*Mean±SD.

infiltrating cells, and the predominance of monocytes/macrophages identified by the PHM2 mAb. Furthermore, the percentage of infiltrating leucocytes was found to differ between grade I and grade II or III tumours, while no significant difference was found between grade II and grade III tumours. The difference between grade I and grade II tumours was explained by a decrease in the percentage of polymorphonuclear leucocytes and T-lymphocytes, but not of monocytes/macrophages.

No difference in the composition of infiltrating leucocytes was observed between unimodal and bimodal tumours, although the latter are associated with the presence of aneuploid cells and a more aggressive evolution. However, the percentage of PHM2 positive cells was slightly higher in bimodal than in unimodal tumours. Since macrophages express the epitope recognised by the SLC1 mAb it is surprising that in bimodal tumours the sum of the percentage of cells stained by ST1, SB3, WEMG1 and PHM2 exceeds that of SLC1 positive cells. It is thus possible that some malignant cells express the PHM2 antigen. Sharing of epitopes between transitional cell carcinoma of the bladder and leucocytes has already been reported. The Leu-M1 antigen which is expressed on 95% of mature granulocytes and 80 to 100% of circulating monocytes was shown to react with 50% of transitional cell carcinomas (Hoshi *et al.*, 1986). The GF26.7.3 antibody, which reacts with a high percentage of bladder and colon carcinomas, cross-reacts with a determinant expressed on neutrophilic cell lineage (Baricordi *et al.*, 1985). Finally, a p50 surface antigen of human urinary bladder carcinomas was found to be expressed by normal and malignant B-lymphocytes (Paulie *et al.*, 1985). Thus malignant transformation of urothelial cells may be associated with the activation of genes which are functional in monocytes/macrophages but not in normal urothelium (Devonec *et al.*, 1989).

The presence of a major leucocyte infiltrate in bladder tumours must be considered in the determination of the DNA profile of a tumour. Classification of tumours as unimodal or bimodal with respect to their cell DNA content should rely exclusively on measurement of tumour cell DNA. The percentage of up to 40% of leucocytes with a DNA index of 1.0 may introduce a bias in the calculation. Some bimodal tumours with a too small percentage of aneuploid cells would be classified as unimodal. Labelling of leucocytes by an anti-pan-leucocyte mAb, or staining urothelial cells with a polyclonal antiserum against several cytokeratins (Feitz *et al.*, 1985), will help to avoid such errors. Leucocytes infiltrating the tumour can be used as an internal standard for the measurement of DNA index and should be preferred to the addition of chicken or trout erythrocytes (Vindelov, 1977) or of the patient's own peripheral blood lymphocytes as proposed by Hiddeman *et al.* (1984).

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Neo-adjuvant Chemotherapy for Invasive Bladder Cancer. Experience with the M-VAC Regimen

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Summary—A series of 71 patients with muscle invasive bladder cancer received a median of 3 cycles (range 1–6) of methotrexate, vinblastine, Adriamycin and cisplatin (M-VAC). Efficacy assessed by transurethral resection alone showed that 48% of patients were T0, 13% Tis and 54% had normalisation of initially positive urinary cytology after treatment. However, when considering transurethral resection of the bladder (TURB), cytology and non-invasive procedures (CT scan and/or ultrasound), only 21% had a clinical complete remission ($_c$CR); 48 patients (68%) had pathological evaluation and 13 (27%) were P0 after treatment. Non-responding patients had a poor prognosis: 14/30 (47%) developed metastatic disease and 13 died. In assessing the primary lesions, clinical understaging was significant. Of 15 patients who were T0 cystoscopically prior to surgery, 6 (40%) had residual disease in the pathological specimen, including 4 with muscle infiltration; 23 patients (32%) remained clinically staged, only 8 of whom remain disease-free. With a median follow-up of 24 months (range 2–42+), 41 patients are alive and disease-free, including 20 with a functional bladder. The large staging error raises questions concerning studies using clinical rather than pathological endpoints as the sole criteria of efficacy.

The increasing number of complete remissions with cisplatin-based chemotherapy (Sternberg and Scher, 1987) for advanced metastatic bladder tumours has led to its use as initial therapy for muscle invasive locoregional disease (Logothetis *et al.*, 1985; Pearson and Raghavan, 1985; Scher *et al.*, 1988; Zincke *et al.*, 1988). Such neo-adjuvant treatment permits an *in vivo* assessment of chemosensitivity, simultaneous treatment of both local and clinically undetected micrometastases (the latter being found in 20 to 40% of high grade lesions) and maximal therapeutic doses of chemotherapy with better patient tolerance (Frei *et al.*, 1987; Raghavan, 1988). Complete tumour regression in the primary lesion in selected cases may also permit bladder preservation.

The preliminary results of our experience using the M-VAC regimen (methotrexate, vinblastine, Adriamycin and cisplatin) in 50 patients with primary bladder (T2–4) lesions have been reported (Scher *et al.*, 1988). We have reviewed the data in 71 cases and noted the potential aberrations in interpreting results of trials which use only a clinical staging (T) endpoint.

Patients and methods

Entry to the study required documentation of a muscle infiltrating tumour by transurethral resection of the bladder (TURB) without clinical evidence of nodal (NO) or metastatic (MO) disease, and adequate haematological, cardiac and renal function (creatinine clearance >55 ml/min/1.73 m^2). The pre-treatment evaluation included abdominal and pelvic CT scans and/or transabdom-

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inal ultrasound, urine cytology and cystoscopic examination with biopsy under anaesthesia. Response was evaluated by cystoscopy and biopsy ("T" stage), by urine cytology and by non-invasive tests (CT scan, ultrasound). All imaging studies and pathology were reviewed independently.

A total of 71 patients received 1 to 6 M-VAC cycles (median 3) as previously described (Sternberg *et al.*, 1988); 47 consented to surgical ("P" stage) evaluation, which included a radical or partial cystectomy, or laparotomy with biopsy via the peritoneal aspect of the bladder at the estimated site of the original tumour, coupled with selected nodal excision or pelvic lymph node dissection. Response was assessed using the criteria of the First International Consensus Development Conference (Yagoda, 1985; Van Oosterom *et al.*, 1986). For assessment of T category, only downstaging to T0 or Tis was considered significant. There were 3 patients in whom all disease was felt to have been resected cystoscopically prior to M-VAC and thus they could not be evaluated for response; however, all were evaluated for time to progression, both locally and systemically.

A clinical complete remission ($_{c}$CR) was defined as complete disappearance of all disease including negative urinary cytology (Table 1). Since all diagnostic procedures were not performed in each case, the number evaluable for each parameter varied. When no tumour was found by TURB (T0) but an abnormality persisted such as positive urine cytology or thickened bladder wall demonstrated by non-invasive staging (CT scan and/or ultrasound), the patient was downstaged to a clinical partial remission ($_{c}$PR). Since tumour regression less than a $_{c}$CR or $_{c}$PR was difficult to document accurately, all other minor responses were classified as incomplete (IR). Pathological staging for this study required surgery within 3 months of completion of M-VAC. Patients in whom no disease was found at definitive surgery were classified as having pathological complete remission ($_{p}$CR); those with less than 3 microscopic foci of tumour, or with remaining *in situ* disease in the surgical specimen, were listed as pathological partial remission ($_{p}$PR) (Scher *et al.*, 1988). The category of complete remission with surgery (CR_s) was not a response category in this trial since most patients were considered resectable at the start of therapy. However, those patients having residual disease at surgery which could be completely resected did receive 2 additional M-VAC cycles. When no effect of chemotherapy was observed pathologically, further therapy was withheld.

Results

Of the 71 patients, 60 (85%) had T3 and T4 disease, and 64 (90%) had a pure transitional cell carcinoma (Table 2). One patient entered the trial with only diffuse Tis disease and 3, who were considered to be resected endoscopically prior to M-VAC, were not evaluable for response. The first clinical restaging was generally performed after the first or second cycle; when tumour regression was documented cystoscopically, additional cycles (median 2, range 1–3) were administered. Cystoscopic assessment after 1 cycle was often difficult to interpret because of residual oedema and reddening. In the latter phases of the study, patients were re-evaluated after 2 cycles of treatment. Five patients received 1, 27 had 2, 8 had 3, 29 had 4, and 2 had 5 or more cycles prior to definitive evaluation.

Of the 71 patients, 6 (8%) were invaluable for

Table 1 Neo-adjuvant Response Criteria

Complete remission (CR)	Disappearance of all tumour by physical examination, radiography, cytologically and cystoscopically both visually and by biopsy, including Tis as defined by the UICC–TNM staging system
Clinical ($_{c}$CR)	Clinically proven
Pathological ($_{p}$CR)	Pathologically proven at laparotomy (Surgical staging may include either a radical or partial cystectomy and/or pelvic lymph node sampling with biopsy of the serosal surface of the bladder)
Partial remission	
Clinical ($_{c}$PR)	(a) > 50% decrease in size of measurable lesions by cystoscopy and/or non-invasive staging with downstaging by 2 or more T categories; (b) T0 cystoscopically, as defined in $_{c}$CR, with a persistent abnormality, *e g* bladder wall thickening by non-invasive staging or persistently positive urinary cytology
Pathological ($_{p}$PR)	[illegible]roscopic foci of tumour or *in situ* disease in the cystectomy specimen, or in the surgical specimen obtained at laparotomy
Incomplete remission (IR)	All other categories of response

Table 2 Details of Patients

No. of patients	71
Age, median (range)	62 years (35–78)
Sex, male:female	63.8
KPS, median (range)	80% (60–90)
Pre-M-VAC clinical stage (%)	
T4	14 (20)
T3	46 (65)
T2	10 (14)
Tis	1 (1)
Initially resected (%)	3 (4)
Pathology (%)	
Transitional cell	64 (90)
Transitional cell	
+adenocarcinoma	2 (3)
+prostatic carcinoma	2 (3)
+squamous cell	2 (3)
Small cell	1 (1)

clinical (T) response because of prior complete resection (3 cases), no TURB prior to laparotomy (2) and initial refusal of further therapy or evaluation (1). In the remaining 65 patients, clinical downstaging to T0 occured in 32 (48%) and to Tis in 9 (13%). Urinary cytology that was initially abnormal became normal in 48 evaluable cases (54%). Using all clinical T parameters of response (cystoscopic, cytological and non-invasive studies), only 14 patients (21%) achieved a complete ($_c$CR) and 26 (39%) a partial remission ($_c$PR): the overall CR+PR response rate was 60% (95% confidence limits, 49–71%).

Clincially staged. There were 23 patients (32%) who refused surgical exploration within 3 months of completing M-VAC; 1 had disease resected at the start of M-VAC and has no evidence of disease at 26 months, leaving 22 evaluable for response (Table 3). Evaluation of therapy revealed that 11 patients (50%) were T0, 7 (32%) had Tis and 4 (22%) remained $\geq$T2. Of the 11 T0 cases, 6 (55%) or 27% of the overall group (6/22) remain disease-free (Table 4) In the remaining 5 cases, 3 developed new *in situ* lesions and 2 were explored 11 and 24 months after developing new invasive tumours; 1 patient had N4 disease and died at 16 months; the other had positive ureteric margins at resection and is alive at 27 months. All patients with recurrent Tis lesions responded to intravesical BCG, but 2 subsequently developed another invasive tumour at 23 and 29 months. At surgery, both had N+ disease. Thus 4/12 T0 patients (33%) eventually developed new invasive tumours with nodal metastases.

Table 3 Stage Following M-VAC Treatment

Staging		*No disease (%)*	*in situ (%)*	*Invasive (%)*
Clinical (T)	22	11 (50)	7 (32)	4 (22)
Pathological (P)	46	11 (24)	4 (9)	31 (67)
Partial	12	6	3	3*
Radical	28	4	1	23
Unresectable	5	0	0	5
Died in CR	1	1		

* Includes 1 with P1 and 2 with P3 disease.

Of the 7 Tis patients, 1 is disease-free 15 months after BCG, 3 continue to have positive cytology at 7, 18 and 22 months respectively, and 3 developed metastatic disease at 6, 8 and 9 months respectively. All M+ patients have died.

Of 4 patients with residual muscle infiltrating tumours, 3 underwent salvage cystectomy at 11, 12 and 18 months respectively and 1 still has invasive

Table 4 Status of Evaluable Patients

Stage after M-VAC	*No of patients*	*Disease-free (%)*	*Recurrent disease (%)*	*Metastatic disease (%)*	*Comments*
Clinically staged					
T0	11	6 (66)	2 (17)	3 (25)	1 died of metastases
Tis	7	1 (15)	3 (43)	3 (43)	3 died of metastases
>T2	4	1 (25)	1 (25)	2 (50)	
Total	22				
Pathologically staged					
P0	11	10 (91)	—	—	1 died in CR
Pis	4	3 (75)	1 (25)*	0	
P1	1	1 (100)	0	0	
>P2	30	15 (50)	1 (3)*	14 (27)	13 died of metastases
Total	46				

* Patients treated with a partial cystectomy.

disease at 18 months. Of note is the fact that 2/4 patients have already developed metastatic disease.

The final clinical (T) evaluation in these 23 patients found 50% T0 (6 ${}_{c}$CR, 5 ${}_{c}$PR) and 32% Tis (${}_{c}$PR); 7 patients have required definitive surgery at a median of 21 months (range 11–29) after the start of chemotherapy and 8 developed metastatic disease, of whom 4 (1 T0, 3 Tis) have died.

Surgically staged. There were 48 patients (68%) who had pathological evaluation within 3 months of completion of chemotherapy; 2 had disease resected at the start of M-VAC and were not considered evaluable for response. In these cases no disease was found at surgery (1 partial and 1 radical cystectomy). One additional ${}_{c}$CR patient died of a pulmonary embolus after 3 cycles of chemotherapy and was found to have no disease (P0) at autopsy. Of 45 cases, 28 had a radical cystectomy, 12 a partial cystectomy and 5 were found to be unresectable. No increase in morbidity was observed in patients who underwent definitive surgery after chemotherapy. None of the patients with atypical histology was P0 at definitive surgery.

Of 11/46 patients (24%±11%) who achieved P0 status after M-VAC, 6 had a partial, 4 a radical cystectomy and 1 (*vide supra*) had no disease at autopsy; 4 showed only Pis after partial cystectomy (3 cases) and radical cystectomy (1). One patient was downstaged to P1 at partial cystectomy and 30 had residual muscle infiltrating disease [2 partial and 23 radical cystectomy, and 5 unresectable], of whom 5 (19%) had N+ disease.

There have been no relapses or deaths in 15 responding patients (10 P0 – ${}_{p}$CR and 4 Pis or 1 P1 – ${}_{p}$PR). Of 2 patients who were resected at the start of therapy and found to have no disease at surgery, 1 is alive at 26 months and the second developed metastatic disease and died at 6 months. In contrast, in the 30 patients with residual invasive disease (25 cases) or unresectable disease (5), 14 (47%) have already developed metastatic disease within a median of 11 months (range 7–17). This includes 10/23 (43%) who underwent complete resection of residual invasive disease by radical cystectomy and 4 of the 5 unresectable cases. One patient with unresectable nodal disease after M-VAC received 4 additional cycles and is alive at 22 months. Of the 2 patients who were rendered disease-free after partial cystectomy, 1 had developed positive cytology at 20 months. Of more importance, 13 of these 30 non-responding patients (43%) have died of metastatic disease.

Staging sensitivity. A comparison of the preoperative T stage and pathological P stage in patients who had a cystoscopic evaluation immediately prior to definitive surgery revealed ${}_{c}$CR in 15 (T0) and ${}_{c}$PR in 5 (Tis). Of 15 T0 patients, 9 (60%) were P0, 1 had Pis, 1 was P1 and 4 were P3. Of 5 Tis patients, 3 were indeed Pis but 2 had a P3 lesion. Thus clinical understaging was found in 6 patients (30%) (4 T0, 2 Tis) who pathologically had residual muscle infiltrating disease.

Correlation of the clinical (T) and pathological (P) responses for 45 evaluable patients (Table 5) found 33 (74%) who were correctly staged ($T = P$) and 8 (18%) who were understaged ($T < P$). Of the 2 ${}_{c}$CR patients who were understaged, 1 had microscopic P1 disease and the other had only microscopic disease in 1 lymph node (P0N1): both remain disease-free. Only 5/14 ${}_{c}$PR cases (35%) were correctly staged ($T = P$). In most cases, the inability to distinguish fibrosis and post-operative changes or viable tumour by a non-invasive staging procedure resulted in over- and under-staging. $T = P$ in all ${}_{c}$IR cases.

Survival. With a median follow-up of 24 months (range 2–42+), 41/71 patients (56%) are disease-free and 20 of these still have a functional bladder. Thus far, 23 of the remaining 30 patients have developed metastatic disease: 8 who were clinically staged (3 as T0, 3 as Tis and 2 as ≥T2), 1 who was resected at the start of M-VAC and pathologically staged as P0, and 14 who were pathologically staged as ≥P3 (${}_{p}$IR). In the latter group, 4 had unresectable disease and 10 residual invasive disease that was completely resected. Overall, 8/23 (32%) clinically staged and 15/48 (31%) pathologically staged patients developed metastatic disease.

Nineteen patients (27%) have died, 18 from metastatic disease; 11 (15%) are alive with disease, including 5 with localised bladder tumours (1 of whom has an invasive lesion), 3 with regional nodal disease and 3 with metastases.

Table 5 Clinical versus Pathological Correlation

	Pathological response			
Clinical response	*No*	${}_{p}$CR (%)	${}_{p}$PR (%)	${}_{p}$IR (%)
${}_{c}$CR	9	7	2	0
${}_{c}$PR	15	4 (27)	5 (33)	6 (40)
${}_{c}$IR	21	0	0	21
Total	45	11	7	27

Toxicity. This was similar to that previously reported (Scher *et al.*, 1988). While no patient died of complications related to chemotherapy, 1 complete responder died, with normal haematological parameters, from a pulmonary embolus after the third cycle. Hospitalisation for neutropenia and fever was required in 9 cases (13%). Haematological toxicity and the number of patients receiving full doses of chemotherapy at the start and days 14 and 21 of a treatment cycle are listed in Table 7.

Discussion

The present study demonstrates that M-VAC alone can induce significant regression of high stage invasive bladder tumours. The overall CR rate was 27% (7 $_{c}$CR+12 $_{p}$CR) with an additional 14% (7 $_{c}$PR+3 $_{p}$PR) of patients being downstaged to superficial *in situ* disease. With a median follow-up of 24 months, 58% are free of disease, including 28% (20/71) with a functional bladder. While the optimal number of cycles has not been defined, responding patients who need additional treatment can be identified after 2 cycles of therapy. Further delays in reassessment beyond 2 months can jeopardise resectability, delay definitive therapy and allow exposure to ineffective treatment.

Table 6 Status of 71 Patients

	No of patients (%)
Alive (no evidence of disease)	41 (58)
Functional bladder	20
Without bladder	21
Alive with disease	11 (15)
In bladder	5
Region nodal	3
Metastatic disease	3
Dead of disease	18 (24)
Died in CR	1 (1)

Table 7 M-VAC Haematological Toxicity

	Cycle 1	*Cycle 2*	*Cycle 3*	*Cycle 4*
No evaluable	68	63	34	32
WBC nadir (cells/mm³)				
Median	3.2	3.8	2.9	3.1
Range	1.1–8.1	1.0–6.8	1.2–7.0	0.8–9.4
Platelet nadir (cells/mm³)				
Median	266	289	303	251
Range	70–528	22–437	112–699	82–801
No. receiving 100% of doses				
No evaluable	71	63	41	35
Day 1–2 (%)	69 (96)	61 (97)	39 (95)	34 (97)
Day 15 (%)	43 (61)	39 (62)	21 (51)	20 (57)
Day 22 (%)	59 (83)	44 (70)	29 (71)	24 (69)
Cycle interval in days				
Median	34	35	36	
Range	28–63	28–57	28–68	

Three groups of patients have been identified. In the first group were 30 non-responding ($_{c}$IR) patients with residual muscle infiltrating or unresectable disease who had a distinctly poor prognosis: 14 (47%) have already developed metastatic disease and 13 (93%) have died. In these cases the role of salvage surgery can be questioned, since most are destined to die of metastases. Similar data have been presented in the EORTC trial of cisplatin and methotrexate, where 7/10 responders remained disease-free while 7/10 non-responders died of metastatic disease during the same follow-up interval (Splinter *et al.*, 1988). Thus the use of neo-adjuvant therapy may allow the *in vivo* identification of a very poor prognostic group, and more aggressive therapeutic approaches may be explored for such patients. In the second group of surgically staged $_{p}$PR patients (4 Pis, 1 P1), only 1 has relapsed with local disease in the bladder; none has developed metastases. In addition, 4/7 $_{c}$PR (Tis) patients have not developed metastatic disease. Resection of residual disease after M-VAC appears beneficial but further data are required. The third group comprised responding patients who achieved $_{p}$Cr status and therefore have a good prognosis. Of 14 patients who were P0 at surgery, only 1 has died.

These data highlight the difficulties in relying solely on clinical staging in the final analysis. After completion of therapy, cystoscopic evaluation revealed downstaging to T0 in 50% (11/22) evaluable clinically staged patients, while only 24% (11/46) were P0 as definitive surgery. In addition 42% (5/11) who were clinically T0 after treatment developed new tumours in the bladder, including 3 with metastatic disease. In contrast, of 11 patients who were pathologically free of disease, 6 after partial and 5 after radical cystectomy, none has developed metastases. Thus reliance on clinical staging alone will tend to underestimate the extent of disease, although it is too early to determine whether this strategy actually jeopardises survival. Also, a "complete" endoscopic resection prior to treatment prevents evaluation of response in the bladder. These patients are receiving therapy in the adjuvant as opposed to the neo-adjuvant setting. For the purpose of these trials, and to minimise exposure to ineffective treatment, complete endoscopic resections should not be routinely performed. This is the policy of the EORTC GU Group (Denis, L., personal communication).

These data also suggest that patients with non-transitional cell components may not be candidates for a bladder preservation approach, since none achieved CR status. Careful pathological evaluation with standardisation of pathological staging procedures is important in this population. Because 20 patients (28% of all 71 and 48% of 41 presently disease-free) are still alive with a functioning bladder at 2 to 42+ months (median 24), bladder preservation could be a realistic endpoint for clinical trials.

Of interest was the efficacy of BCG for treatment of residual (1 case) or new *in situ* disease (3 cases). All 4 patients responded, although 2 developed muscle infiltrating disease at different sites 21 and 24 months later. Continued careful follow-up is required in these patients, since bladder preservation may only delay the time to cystectomy and in some cases this strategy may jeopardise survival. Furthermore, patients at risk of developing new lesions can be considered for chemotherapy or immunopreventive trials.

Recognising that M-VAC, like most other systemic cisplatin-based chemotherapeutic regimens, is inactive against carcinoma *in situ* the neo-adjuvant response criteria listed in Table 1 may be too rigid. Some superficial disease is considered non-lethal and the rationale for neo-adjuvant chemotherapy is to control muscle invading disease, which does metastasise. Thus it may not be unreasonable to include ${}_{p}$IS in a complete response category.

The results also raise questions about techniques of analysis. In the present study, patients were considered to progress when new metastatic or local disease was documented. The latter may not represent a failure of neo-adjuvant therapy. All sites of progression, local and systemic, must be evaluated. In selected patients, bladder preservation is safe and feasible, but the ultimate endpoint for neo-adjuvant trials must remain survival.

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B5 Tumour Marker and Urine Cytology in Diagnosis and Follow-up of Transitional Cell Bladder Cancer

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Summary—The correlation between a new tumour marker, B5, and tumour behaviour in bladder cancer was recorded and an assessment made of the value of combining the B5 test with urine cytology for predicting the presence of tumour. The study group included 57 new patients, of whom 32 were B5 positive at diagnosis and were well marked by B5 on follow-up. There were no false positive shifts in new patients who became free of observable tumour, whilst 1 of 13 patients with persistent disease showed a false negative shift. When the findings from 199 cystoscopies were compared with the results of B5 and urine cytology, B5 was found to improve the prediction of recurrent tumour over cytology alone. Moreover, a high incidence of occult malignancy (7/19) was found in patients where cystoscopy had failed to show recurrence but whose combined marker results were both positive.

Endoscopic and radiological surveillance for patients with transitional cell bladder cancer is prolonged, time-consuming and may place some with intercurrent disease at risk from anaesthesia if undergoing rigid endoscopy. Although the follow-up programme for an individual may be modified according to symptoms, tumour grade, invasiveness and recurrence rate, additional information from tumour markers might be helpful not only in selecting patients for endoscopy but also in warning of occult tumour. A new tumour marker has been described which reflects a change in the surface of autologous erythrocytes and is associated with the development of cancer, regardless of tumour type (Milner and Metcalfe, 1982). This change can be detected by a simple haemagglutination test and it has been found that B5 status often moves with tumour status, becoming more negative after successful treatment, or more positive in relapse (Metcalfe and Jones, 1987 and unpublished observations). Results from a double-blind study of bladder cancer patients (Metcalfe and Jamieson, 1984) suggested that the B5 test might provide a useful adjunct to the routine clinical management of disease. To investigate this further we analysed 154 patients, including 57 new patients, to determine the extent of B5 correlation with disease behaviour and to ask whether a combination of the B5 test with urine cytology improved the predictive value of tumour presence when compared with urine cytology alone.

Patients and Methods

New patients

Over a 30-month period, starting in 1984, 57 consecutive new patients were referred to Weston General Hospital with transitional cell bladder tumours. Pre-operative assessment and routine investigations included a mid-stream urine examination, urine cytology and intravenous urography. B5 levels were also measured; blood samples were collected into 5 ml Liheparin tubes and posted to Cambridge for assay.

Patients on follow-up

After initial diagnostic cystoscopy and resection of tumour, endoscopic follow-up and treatment varied according to tumour grade and invasiveness. More superficial tumours were cystoscoped at intervals of 3, 6 and 12 months after initial resection and thereafter at varying intervals depending on tumour

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behaviour and response to treatment. More aggressive tumours (T3 and T4) were usually treated by external irradiation, progressing to cystectomy within 12 months for persistent or recurrent local disease. All patients attending follow-up were tested for B5 status and had a urine cytology examination during the week prior to cystoscopy.

Cytology

Fresh urine was sampled in triplicate (0.5 ml each) and cells centrifuged on to glass slides by cytocentrifugation. Two slides were wet fixed in methanol before staining with haematoxylin and eosin; the third slide was air dried, fixed as before, and stained with May-Grunwald Geimsa. All cytology slides were screened by a trained medical laboratory scientific officer. Those showing any abnormality were examined by the pathologist who made the reports. The results are now presented as either positive or negative, with intermediate interpretations of dysplasia or other features suggestive of malignancy being regarded as negative. This assignment did not introduce undue bias to the results, the actual numbers with uncertain cytology being 7/57 in the new patients, 16/74 in those with recurrent tumour, and 18/69 in patients with a "clear" cystoscopy.

B5 assay

All B5 assays were performed in Cambridge upon receipt of samples. A small aliquot (approximately 100 µl) was washed twice in 20 ml phosphate buffered saline (PBS, pH 7.4) at room temperature; 10 µl of packed erythrocytes were then diluted to 1% in 1 ml PBS containing 4% fetal calf serum; 20 µl of these 1% cells were mixed with 25 µl of B5 antibody (standard titre) in a 'U' well haemagglutination plate. The plates were covered with film and left at least 2 h before reading. Haemagglutination was scored positive or negative using an inverted microscope to view the pellets directly under low power. Each sample was also scored by microscopic examination of cells gently resuspended and transferred on to a glass slide; here the cut-off between positive and negative was taken at cell clumps which involved 20 or more erythrocytes (positive), with anything less being scored negative. The percentage free cells was also estimated and used to plot the results. Each sample was scored blind twice by 2 workers and any reading which showed a discrepancy of more than 10% led to a repeat assay of the sample: the need to reassay was rare. During the course of this study repeat samples from a wide variety of controls confirmed the high level of reproducibility of the B5 assay, including repeated testing of a single control donor at different times and multiple assays on a single sample. Several other centres have found the assay to be simple and robust (Tuck *et al.*, 1985; Bruce *et al.*, 1987). It is relevant to note that when B5 haemagglutination is read on an optical density automated readout, using blood cross-matching methods, there is a very good correlation between visual and automated scores for a given sample, so confirming the accuracy of the visual readout. In this study all assays were read microscopically.

Results

Does B5 correlate with tumour in the new patient group?

At diagnosis 32/57 patients were B5 positive. There was no clear correlation between B5 positivity and the age or sex of the patients, with the histological grade or with the invasiveness of the tumour. This group of patients was also analysed on follow-up to establish any relationship between B5 behaviour and tumour behaviour, and the results for 45 patients are summarised in Figure 1. In Figure 2 the B5 score at diagnosis, and then at follow-up, is shown for each patient: the patients were grouped according to their B5 status at diagnosis and to the clinical progress of disease. Most of the patients (11/15) who were scored B5 positive at diagnosis, and who subsequently became disease-free (Fig. 2A), showed a negative B5 shift. In contrast, 6/7 patients who were B5 positive at diagnosis, and

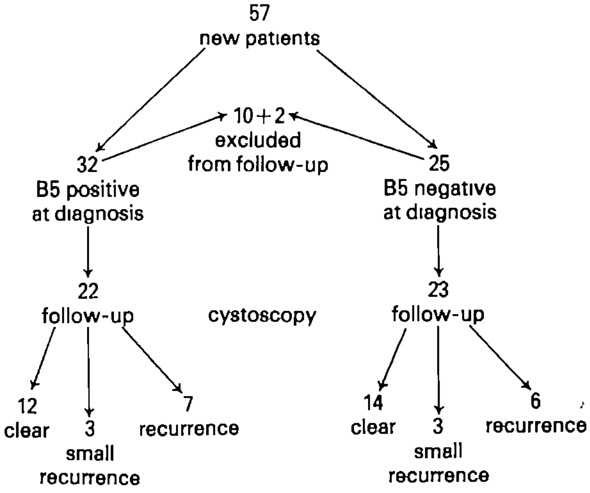

Fig. 1 B5 status of 57 consecutive new patients at diagnosis; 45 were followed up by cystoscopy for 6 months or more and the result of cystoscopy on first follow-up is shown. "Small recurrence" is single tumour less than 3 mm in diameter

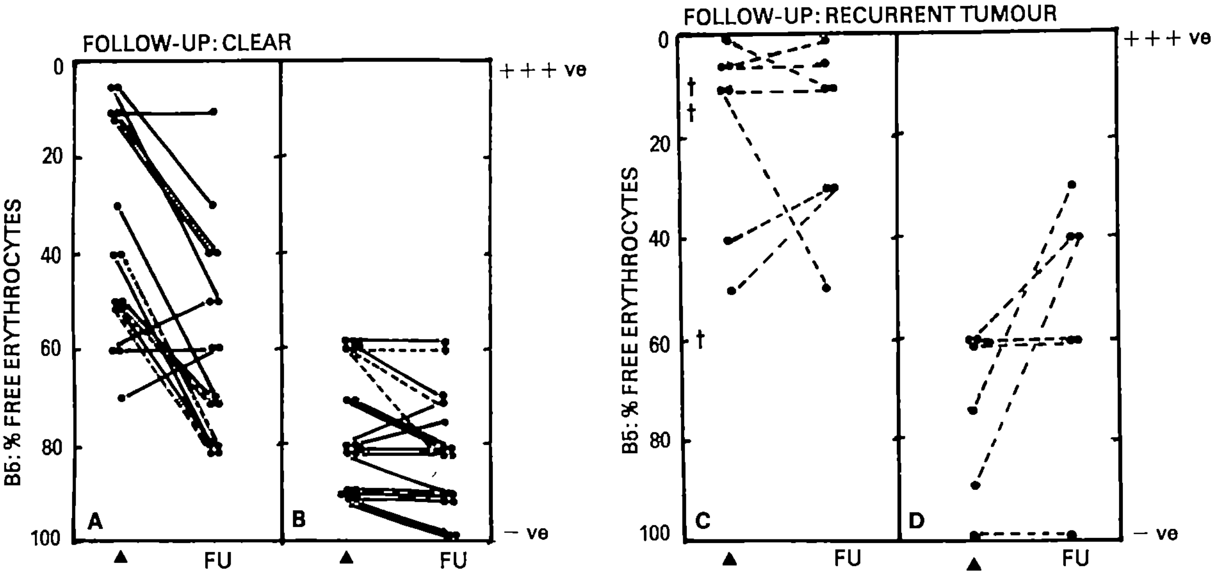

Fig. 2 Changing B5 status of individuals at diagnosis and follow-up grouped according to result of first follow-up cystoscopy. The percentage free cells for each patient at diagnosis is joined to the score at follow-up. The cut-off between positive and negative was where clumps of 20 or more erythrocytes were seen and usually coincided with a percentage free score of 60 to 70%. Hence at diagnosis A and C were positive, B and D negative. Dashed lines in A and B indicate small recurrence at first follow-up, none at second. † indicates early death after diagnosis.

who had persistent or recurrent disease, showed a strong positive, or increasingly positive, B5 status (Fig. 2C). Of the 23 patients who were B5 negative at diagnosis, 18 became free of observable tumour by 6 months (15 by 3 months): these 18 patients remained B5 negative (Fig. 2B). The 5 remaining patients all had invasive tumours which were irradiated and 3 who progressed to surgery showed a positive shift in B5 status (Fig. 2D).

The 12 patients who were excluded from the follow-up study consisted of 3 who died within 6 months of diagnosis (Fig. 2C), 1 who had presented with rib metastases, 1 who declined follow-up, 4 with insufficient follow-up and 1 who had been previously treated for rectal cancer in addition to having a second colonic carcinoma diagnosed 5 months after presenting with bladder tumour (his strongly positive B5 status may have reflected either or both tumours). All of the 10 patients listed so far were B5 positive at diagnosis. The 2 remaining patients had been B5 negative; 1 underwent total cystectomy for intractable bleeding associated with multiple Grade II tumours and the other patient moved out of the region after initial treatment.

The B5 status of 3 patients on follow-up is presented in detail in Figure 3 as an anecdotal illustration of how this marker may behave in the course of the disease.

Does a combination of B5 and urine cytology improve the predictive value of urine cytology alone?

In the second part of this study, B5 and urine cytology were combined and an assessment made of whether the dual markers altered the predictive value of the cytology for recurrent tumour. The 57 new patients were scored at diagnosis and 45 of these were scored again at their first follow-up cystoscopy. The rest of the observations were made during the early part of the same period on 97 patients undergoing routine follow-up cystoscopy for bladder tumour. They were unselected and simply added to the series sequentially on the first occasion that B5 and urine cytology were performed.

Table 1 shows the B5 and cytology results for the new patients at diagnosis and for the 142 follow-up cystoscopies which have been grouped according to the cystoscopy result. Table 1a shows that of 57 patients undergoing diagnostic cystoscopy, 32 (56%) were positive for both B5 and cytology; of these patients 5 (8%) were double-negative; 3 had Grade II tumours, 1 had a very small Grade I tumour and 1 had a Grade III tumour. On follow-up, 1 of the Grade II patients showed a marked increase in B5 positivity; this was associated with a rapid growth of the tumour, which failed to respond to radiotherapy.

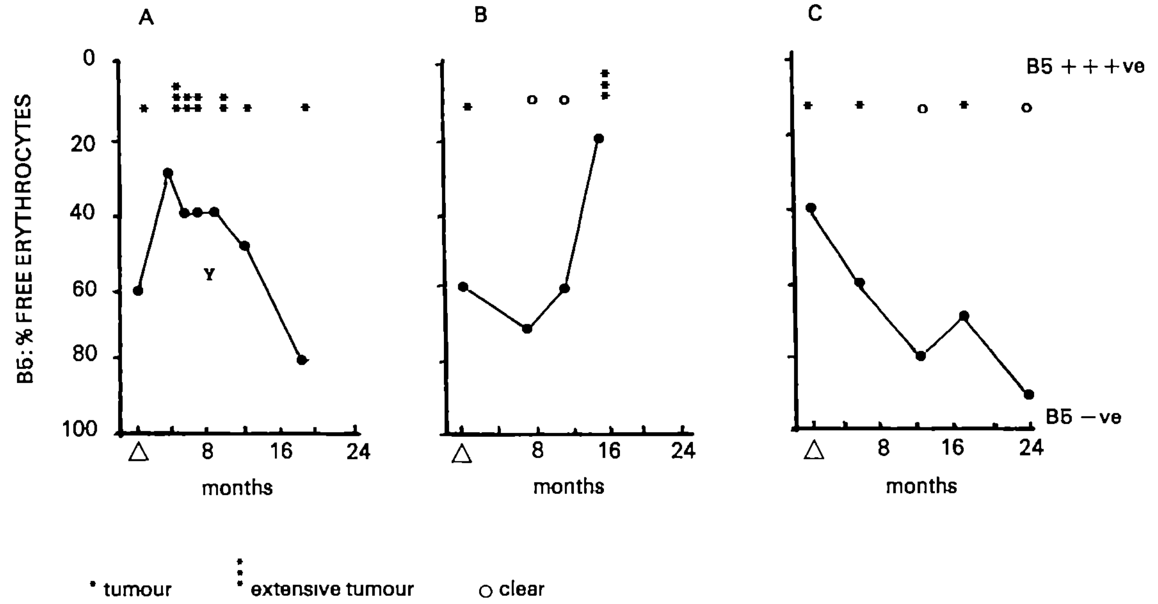

Fig. 3 B5 graphs and summaries of 3 patients monitored from diagnosis (A) Grade III tumour—multiple recurrences at 3 and 9 months, then treated with colloidal yttrium. No recurrence at 17 months. (B) Grade III invasive tumour, radiotherapy. No recurrence in bladder at 7, 11 and 15 months but metastatic tumour apparent. (C) Two tumours Grades II and III Small recurrence at 5 and 17 months, none at 24 months.

The follow-up patients with visible recurrent tumour are shown in Table 1b; 30/69 (43%) were positive for both markers at the time of the tumour's recurrence; 7/69 (10%) were double-negative; 2 had Grade I recurrence, 4 had Grade II small recurrences and 1 had multiple recurrences, some of which were Grade III.

In those patients who were found to be tumour-free by cystoscopy (Table 1c), 21/73 (29%) were negative for both markers and 19 (26%) were double marker positive (Table 2a). The latter group included 7 patients who were subsequently found to have concurrent malignancy elsewhere in the urinary tract and 4 who produced visible tumour in the bladder seen at cystoscopy 3 months later. To determine if this high incidence of occult tumour

Table 1 B5 and Cytology of New and Follow-up Patients According to Result of Cystoscopy

(a) 57 new patients at diagnosis			
	B5+	B5−	
Cytology +	32	18	i.e 32/57 double positive
Cytology −	2	5	5/57 double negative
(b) 69 follow-up cystoscopies—recurrent tumour seen			
	B5+	B5−	
Cytology +	30	18	i.e 30/69 double positive
Cytology −	14	7	7/69 double negative
(c) 73 follow-up cystoscopies—no tumour seen			
	B5+	B5−	
Cytology +	19	18	i e 19/73 double "false" positive*
Cytology −	15	21	21/73 double negative

* See Table 2.

Table 2 Fate of Patients with Negative Follow-up Cystoscopy But Positive Markers

(a) Patients who had a negative cystoscopy but who were double positive for B5 and cytology

7/19 had concurrent malignancy

i.e. 2 non-invasive carcinoma *in situ* on random biopsy.
1 new transitional cell carcinoma in the renal pelvis
1 ureteric tumour
1 adenocarcinoma of the kidney
1 recurrent bladder tumour outside the bladder
1 carcinoma of the prostate

4 later developed recurrences

i e. 2 invasive Grade III recurrences
2 non-invasive recurrences

8 remain tumour-free (up to 3 years) and have become negative for one or other marker

(b) Patients who had a negative cystoscopy, who were B5 negative but who had a *positive* cytology

3/18 later developed tumour

i e 1 carcinoma *in situ*
1 Grade II non-invasive recurrence
1 Grade III invasive recurrence

15 remain tumour-free (18 months)

related to the double marker positivity rather than reflecting a background incidence, we also looked at the fate of 21 patients whose markers were both negative and who had had a negative cystoscopy. No occult tumours were found in this group, although in 1 patient a transitional cell carcinoma of the renal pelvis was seen 3 months later, when cytology became positive.

In addition to analysing patients according to the result of cystoscopy, we also looked at all patients undergoing follow-up cystoscopy to discover to what extent the combined markers might have predicted the clinical findings (Table 3). In over 50% of patients both markers were in agreement—either both positive or both negative. Of the 49 patients who were double positive, 37 (76%) had concurrent tumour; 28 patients were double marker negative and 7 of these (25%) had tumour, 1 of which was Grade III; the other 6 patients became tumour-free by their next follow-up visit.

Using cytology alone as a guide to the presence of recurrent tumour, there was a 59% correlation with the disease status, 48/69 patients (70%) being positive with recurrence and 36/73 (49%) negative without disease. Thus for patients who were double marker positive or negative there was a significant improvement in specificity and sensitivity for disease since 37/44 (84%; results correct for occult tumour) double positive patients had active disease and 21/33 double negative patients (64%) were disease-free. For those patients who had 1 marker positive only, there was no significant difference between B5 and cytology in specificity and sensitivity for disease on follow-up: a finding of note was that cytology alone did not show a predictive value for occult tumour (Table 2b).

Table 3 B5 and Cytology Status of All Patients on Follow-up

	B5+	*B5−*
Cytology +	49*	36
Cytology −	29	28†

*49 double positive
  30 had recurrence seen by cystoscopy
  7 had unsighted tumour or carcinoma *in situ*
  4 had recurrence seen at next follow-up cystoscopy
  4 had had other malignancies (1 skin,
  1 colon 1 uterus and 1 prostate) in the past
  4 remained tumour-free and became cytology negative
† 28 double negative
  20 were clear of tumour and remained so
  7 had visible recurrence (6 became clear by next follow-up cystoscopy)
  1 had unsighted tumour 3 months later

Discussion

Indirect tumour markers can be helpful as a minimally invasive diagnostic and monitoring aid in the management of cancer patients. Some such markers, either in blood or urine, have been assessed as aids in the management of bladder cancer patients (Javadpour, 1978). In this role urinary carcinoembryonic antigen (CEA) levels appear more reliable than serum CEA levels (Zimmerman *et al.*, 1980), although they are also elevated in infected urine irrespective of tumour behaviour. Other indirect markers of bladder cancer include alphafetoprotein and fetal haemoglobin (Alsabti *et al.*, 1978), tissue polypeptide antigen (Kumar, 1981), urinary cancer-related protein (Chawla *et al.*, 1978) and urinary immunoglobulins; these are all of dubious value.

Following the discovery of the B5 tumour marker in 1982, a study in bladder cancer patients in Cambridge showed good correlation between the presence of new (18/20) or recurrent (41/54) cancer and B5 positivity (Metcalfe and Jamieson, 1984). The natural incidence of B5 positivity in healthy controls is approximately 18%: monitoring of control subjects has shown that each individual's B5 status remains constant and the only known cause of a positive shift in B5 status is the development of cancer. So, for the individual, monitoring of B5 status is more informative than a single measurement and here we have included B5 measurements in the follow-up of bladder cancer patients.

In the present study, 32/57 patients were B5 positive at diagnosis: thus there was a lesser correlation between the B5 marker and disease than had been found in the Cambridge study. This variation in results may be explained by our monitoring data, which revealed 2 groups of patients: those who were B5 positive at diagnosis and who appeared to be well marked by B5, and those who were B5 negative at diagnosis, where only 3 of 6 patients with persistent disease were marked by an upward shift in B5 status. The observed shifts in B5 status correlated well with disease status in that there were no false positives and only 1 of 13 patients with persistent disease showed a false negative shift.

When B5 was combined with urine cytology there was no improvement in diagnostic indication. However, for patients on follow-up the addition of the B5 test provided a valuable adjunct to cytology since specificity and sensitivity for concurrent tumour were improved in over 50% of case. An unexpected finding was the high incidence of tumour in patients who were apparently clear of disease on cystoscopy but who were positive for both markers. These positive marker results led to 2 patients having repeated upper tract investigations, when occult tumour was found, and to 6 others being called back for early re-investigation, resulting in the discovery of tumour.

In conclusion, the B5 marker appeared to correlate with bladder cancer, particularly in patients who were B5 positive at diagnosis. We have no explanation as to why some patients did not appear to have their bladder tumour marked by B5, since no common feature was detected. The combined use of B5 and urine cytology enhanced marker specificity for bladder cancer in over half of the patients on follow-up. When both markers are positive, although no tumour is seen in the bladder, further investigation is likely to reveal occult tumour.

Acknowledgment

We are indebted to Dr M. E. H Halford, who performed routine cytological investigations on all patients in this study.

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Scintigraphic Assessment of Lower Urinary Tract Function in Children With and Without Outflow Tract Obstruction

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Summary—Analysis of lower urinary tract function with an extension of standard renography with ^{123}I-hippurate was carried out in 199 children.

Maximum bladder capacity, voiding and residual bladder volumes, average and maximum urine flow rates and urine flow patterns were estimated. The index of urine transport (IUT), representing the relationship between urine flow rate and bladder volume, was introduced as a measure of outflow capability.

Of 129 children without evidence of outflow obstruction, 90% had a normal urine flow pattern; in 96% the average IUT was 0.8 or higher and in 87% the maximum IUT was 1.2 or higher. A sawtooth-shaped pattern with both normal and abnormal IUT values was observed in 10% of these children.

In 63% of the children with outflow tract obstruction there was a low, flat urine flow pattern together with decreased IUT values. A sawtooth-shaped pattern with varying IUT values was observed in 15%, whereas in 20% the urine flow pattern and IUT values were normal.

This extension of standard radionuclide renography as a method of screening lower urinary tract function is recommended. It is at least as good as conventional direct urine flow rate recording, it has the advantage of being non-invasive and it is also part of an established urological investigation.

Although many techniques are used to assess the upper and lower urinary tract, there is no agreement about the best sequence of investigations in children with urinary tract infection (Merrick *et al.*, 1982; Haycock, 1986). In general, radiologists recommend urography and contrast urethrocystography, and urologists also include urethrocystoscopy.

In screening children with urinary tract infection or other urinary problems it is desirable to use non-invasive methods with low radiation and considerable accuracy. Ultrasonography provides reliable information on the anatomy of the upper and lower urinary tract but no information on renal function. The results of this method depend on the performer's experience. Urodynamic studies (using transducers) with measurement of flow rates in relation to bladder volume, bladder pressure and voiding patterns are popular as a screening procedure and in assessing the results of treatment or progression of disease of the lower urinary tract.

Scintigraphic methods are well established. DMSA (^{99m}Tc dimercaptosuccinic acid) renal scintigraphy is used for diagnosing pyelonephritis and estimating differential renal function; intravenous renography extended by voiding cystography (IRVC) is used for screening the upper urinary tract, the competence of the ureteric orifice and in estimating residual volume and average urine flow rate (Merrick *et al.*, 1979; Pollet *et al.*, 1981).

We present a further analysis of the voiding part of IRVC. The usefulness of the index of urine transport as a measure of outflow capability was evaluated in children with and without outflow tract obstruction.

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Patients and Methods

Children were investigated under physiological conditions so that bladder filling and emptying could be effected in a natural way. A relaxed atmosphere was created and attempts were made to increase the child's privacy during voiding. Renography was carried out in the prone position on a specially constructed commode chair. When micturition occurred, data were registered with the patient remaining in the same position for 90 s.

Patients were asked to void at the start of the investigation. A forced diuresis was then achieved by oral water load at a rate of 20 ml/min. Renography was started 10 to 30 min later after the intravenous administration of 10 to 20 MBq ^{123}Iodide-hippurate. An acquisition time of 40 min was used, but interrupted within this time limit when a spontaneous urge to void was expressed and could no longer be resisted. Data acquisition during voiding took place at 1-s intervals for a total of 90 s.

A large field of view gamma camera, equipped with a general purpose parallel hole collimator and connected to a computer system, was used. Instrumentation, data acquisition, calculation of data, normal values and evaluation of the reliability of the method have been described in detail by van der Vis-Melsen *et al.* (1988).

Definitions of the measured data conform with the standards proposed by the International Continence Society (Abrams *et al.*, 1988) and are as follows:

Maximum bladder capacity: the volume at which the patient has a strong desire to void.
Voided volume: the total volume expelled via the urethra.
Flow time: the time over which measurable flow actually occurs.
Average flow rate: voided volume divided by flow time.
Maximum flow rate: the maximum measured value of flow rate.

This investigation included 199 children (138 girls and 61 boys). Their ages ranged from 2.5 to 18 years, with 93% being under 15 years.

The indications for their referral are listed in the Table. Three groups were identified:

Table Indications for Referral

	Group I	*Group II*
Urinary tract infection	62	29
Vesicourethral reflux		
Recently diagnosed	3	1
Follow-up	7	—
Post-operative	2	—
Abnormal contrast urography	10	3
Nocturnal enuresis	33	11
Abnormal micturition history	—	7
Hypospadias	—	4
Urethral valves	—	3
Miscellaneous	12	2
Total	129	60

Group I. In 129 children there was no clinical evidence of lower tract pathology. In 37 cases this was confirmed by retrograde contrast micturition urethrocystography and/or urethroscopy; these we called "true normals". In the other patients invasive diagnostic tests of the lower urinary tract were not clinically indicated. While all children were evaluated for some kind of urinary tract problem, this group cannot be considered representative of the general population, but ethical considerations regarding radiation prevented us from obtaining true normal values in children without urinary tract pathology.

Full urodynamic analysis (pressure/flow studies) in order to exclude or assess outflow obstruction was not available.

Group II. In 60 patients outflow tract obstruction was diagnosed by cystourethroscopy (in 23 of them contrast micturition urethrocystography was also performed).

Group III. Ten patients were investigated only after surgical intervention for lower urinary tract obstruction.

None of the patients was studied during or immediately after acute infection of the urinary tract.

The effective dose equivalent per unit of administered radioactivity for pure ^{123}I-hippurate and normal kidney function is: 0.05 mSv/MBq for age 5 years, 0.035 mSv/MBq for age 10 years and 0.03 mSv/MBq for age 18 years (Marcus and Kuperus, 1985).

Results

Renography extended by voiding cystography provided information on upper urinary tract function and the competence of the ureteric valve, as demonstrated in 3 patients (Figs 1–3).

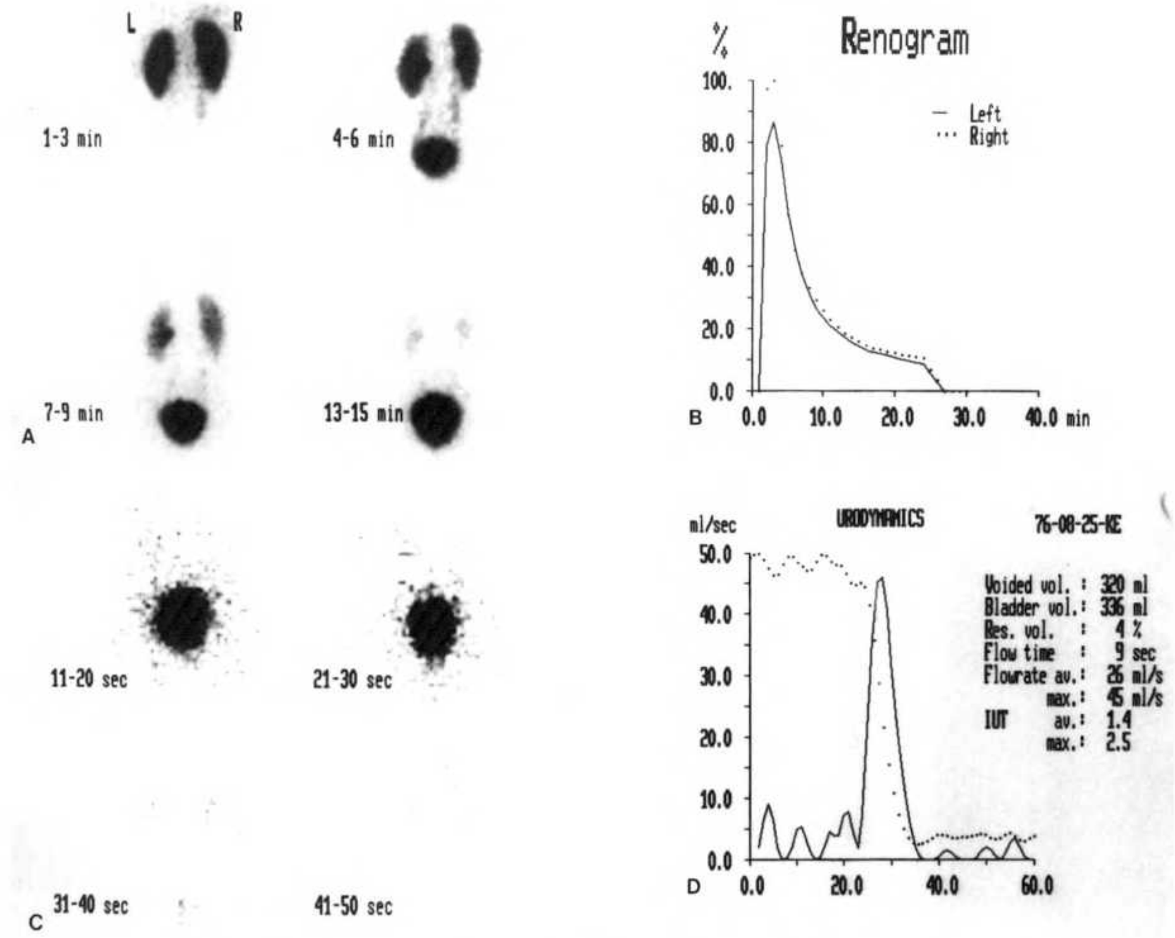

Fig. 1 Normal intravenous renography/voiding cystography of 10-year-old girl with recurrent urinary tract infections. (A and B) Renography. Selection of summarised sequential images and time activity curves of both kidneys. (C and D) Micturition. Voiding images, bladder emptying curve (dotted line) and urine flow rate curve (uninterrupted line) with the different parameters.

Urine flow patterns

In analysing urine flow patterns we recognised 4 distinct patterns: a single sharp peak (Fig. 1), a biphasic form, a sawtooth-shaped model (Fig. 2) and a low flat curve (Fig. 3). In children without outflow obstruction (Group I), the first 3 patterns were observed in 70, 20 and 10% respectively. In children with outflow obstruction (Group II), all 4 patterns were observed in 10, 12, 15 and 63% respectively (Fig. 4).

Urine flow rate

Average and maximum urine flow rates were established in each child.

The relationship between urine flow rate and bladder volume was expressed as the ratio of flow rate and square root of bladder volume (known as the index of urine transport (IUT)). Average and maximum IUT values for patients of both groups are listed in Figure 4.

Group I. The mean maximum IUT for all children was 1.7 (SD 0.5); the mean average IUT was 1.3 (SD 0.5). Compared with the values of the 37 "true normals", a maximum IUT of 1.2 or higher ($P<0.005$) and average IUT of 0.8 or higher ($P<0.005$) were considered normal.

Of 116 children with a normal or biphasic urine flow pattern, 5 had both average and maximum IUT values below normal, whereas in 7 children only the maximum IUT value was slightly decreased.

Of 13 children with a sawtooth-shaped pattern, 5 had normal average and maximum IUT values;

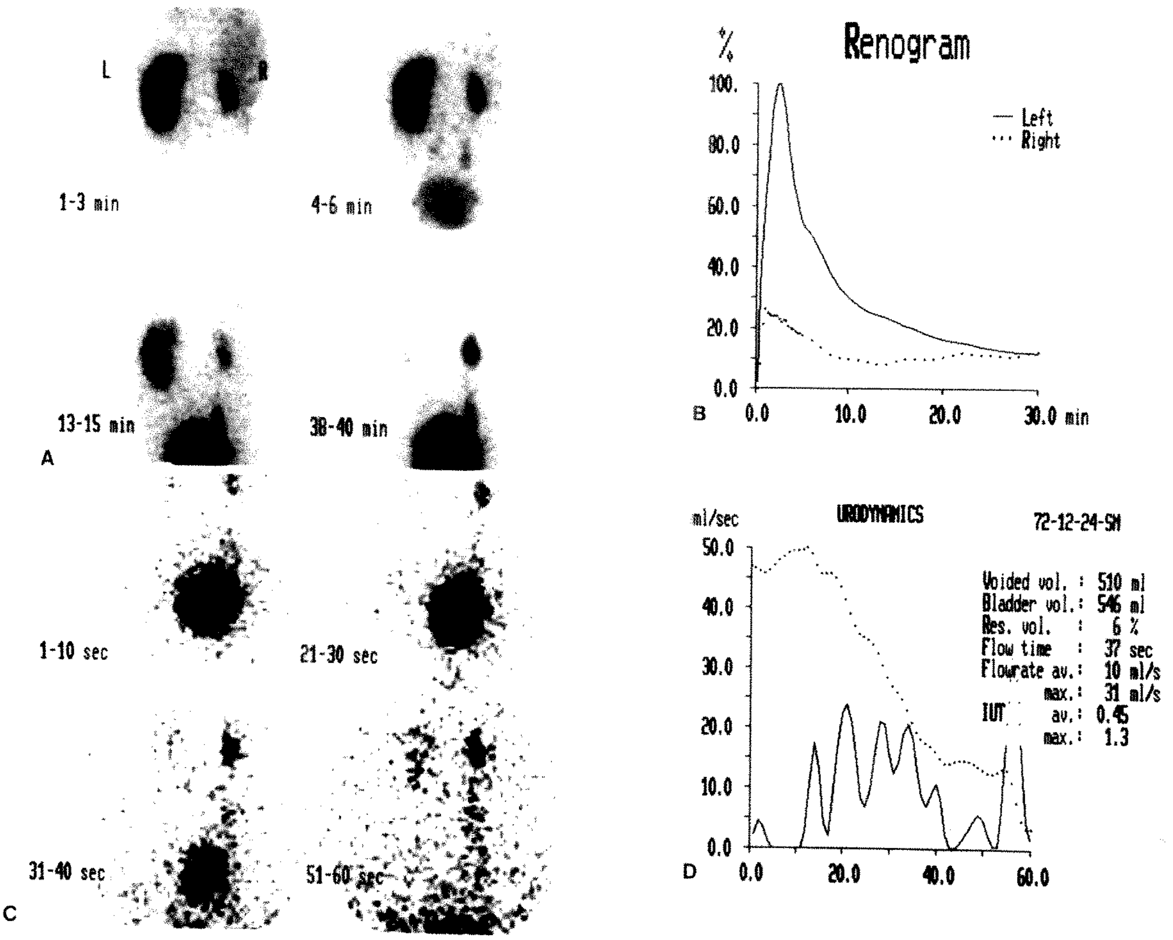

Fig. 2 Results in 15-year-old girl with recurrent urinary tract infections. (A and B) Renography. Enlarged left kidney with normal function. Small right kidney with loss of function and vesico-renal reflux pre-voiding. (C and D) Micturition. Slight vesico-renal reflux on right side during voiding. Sawtooth-shaped voiding pattern with low average IUT and normal maximum IUT.

in 4 children both values were decreased and in another 4 only the average IUT was below normal.

Group II. In 38 children with a low flat (obstructive) voiding pattern, both the average and maximum IUT values were below normal.

A sawtooth-shaped pattern was observed in 9 patients: in 5 of them both average and maximum IUT values were decreased; in 2 cases both were in the normal range; in 1 the average IUT was normal but the maximum IUT was decreased, and in 1 the average IUT was below normal but the maximum IUT was normal.

In 13 patients with a normal or biphasic urine flow pattern both IUT values were in the normal range.

Residual volume

Residual volume was not expressed in absolute terms (ml) but as a percentage of the measured bladder volume. Less than 9% residual volume was considered normal ($P < 0.05$), 10 to 15% residual volume was considered equivocal and values exceeding 15% were abnormal.

Reliability and reproducibility

Reliability of the method was evaluated in 10 patients by simultaneous registration of the urine flow with a transducer uroflowmeter. Voiding patterns were identical. The difference in average flow rate figures was negligible, although the results for maximum flow rate showed a slight discrepancy. Unfortunately, reproducibility could not be

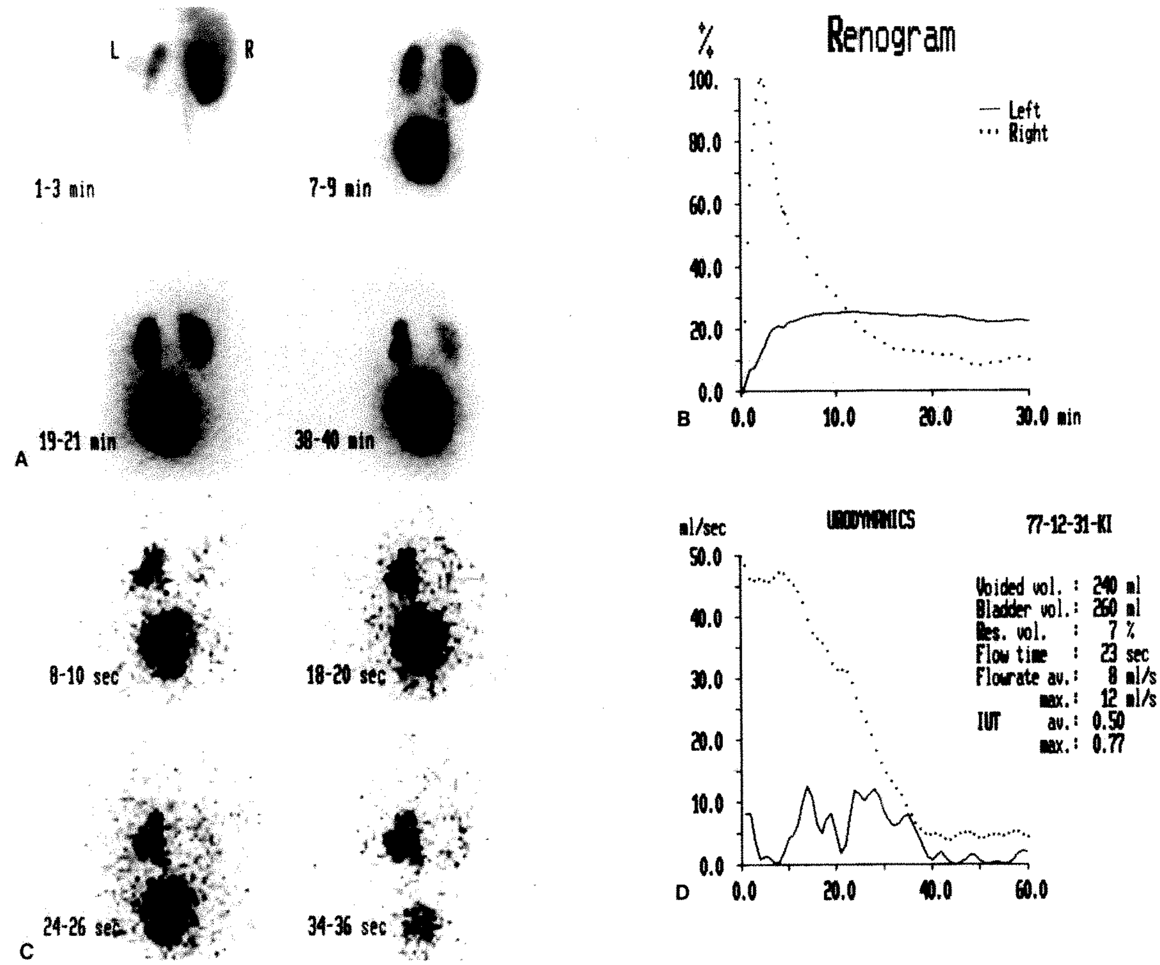

Fig. 3 A 9-year-old boy with enuresis. (A and B) Renography. Small left kidney with loss of function and delayed washout. Normal right kidney. (B and C) Micturition. Vesico-renal reflux on left side during voiding. The voiding pattern is flat with low average and maximum IUT values.

checked because ethical considerations prevented us from repeating the investigation in the same patient on a different occasion without due cause. However, 12 patients voided twice during the same investigation. In 9 of these there was only a slight difference in some of the parameters, but in 3 cases the results of all parameters were quite different.

Discussion

In analysing micturition one must realise that the act of urination is a highly individual function, varying not only in different patients but also in the same patient on different occasions and under different circumstances. Voiding efficiency is a matter of balance between voiding forces and outflow resistance, and a disturbance of either may result in outflow obstruction (Turner-Warwick *et al.*, 1973; Farrar *et al.*, 1976).

In identifying criteria of an anatomical cause of outflow tract obstruction there are many difficulties. Evaluation of meatal and urethral abnormalities by symptomatology, clinical examination, radiographic studies and endoscopy is of limited value (Turner-Warwick *et al.*, 1973).

Urodynamic evaluation by combined pressure and urine flow measurements is widely accepted in determining voiding efficiency and in identifying outflow obstruction (Turner-Warwick *et al.*, 1973). The advantage of this technique is the simultaneous measurement of bladder pressure, urine flow rate and residual volume; the disadvantages are bladder catheterisation and retrograde bladder filling. Apart from the risk of introducing infection, these

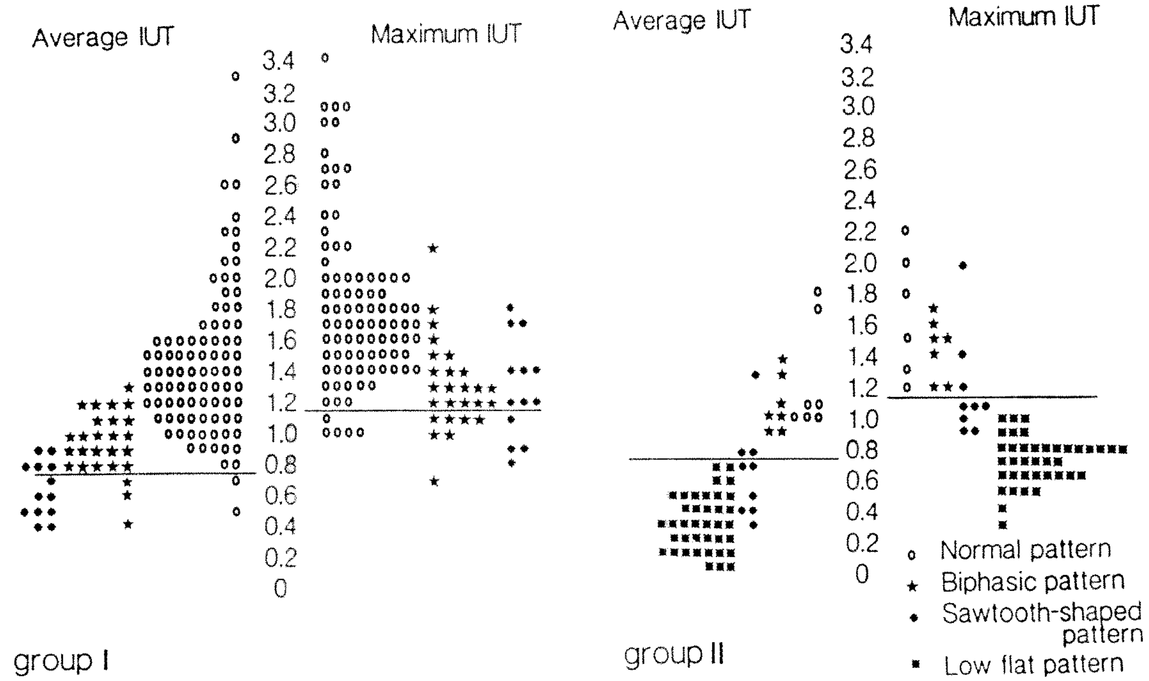

Fig. 4 Distribution of voiding patterns, average and maximum IUT values for children without (group I) and with (group II) outflow obstruction of the lower urinary tract.

procedures are traumatic (particularly in children) and interfere with a physiological assessment of bladder function.

Isolated urine flow measurement with or without catheterisation has its limitations (Abrams *et al.*, 1988): differentiation between abnormal detrusor function and an anatomical cause of outflow obstruction is impossible (Taylor *et al.*, 1982). However, Farrar *et al.* (1976) and Hjälmas (1977) suggested that measurement of both the peak voiding urine flow rate and the urine flow rate in relation to bladder volume was satisfactory as a functional screening test of the lower urinary tract.

We have determined the ratio between urine flow rate and square root of bladder volume as a measure of outflow capability as proposed by Hjälmas (1977). This index of urine transport was estimated for both average and maximum urine flow rates. An average IUT of 0.8 or higher and a maximum IUT of 1.2 or higher were considered normal and were found in 96 and 87% respectively of children without evidence of outflow tract obstruction. Both a single sharp voiding peak and a biphasic flow pattern (observed in 90% of children without evidence of outflow tract pathology) were considered to be normal voiding patterns. We did not find a low flat voiding curve in our normal population.

Using the results of urethrocystoscopy in excluding lower urinary tract obstruction (37 "true normals"), our method failed in 8% of the children. If one considers that moderately decreased urine flow ratios in children with a normal or biphasic flow pattern in group I may be caused by a poorly contracting bladder or some hesitation during voiding, this percentage might be lower.

In 13 patients in group II with a normal or biphasic voiding pattern, IUT values were in the normal range. In 9 of these patients the outflow tract on contrast urethrocystography was considered normal. In 1 patient, urine flow analysis performed on a different occasion in the Department of Urology with a transducer uroflowmeter was also normal. In another patient there was only a slight suspicion of a urethral valve. In view of the varying results in most of these patients, the lack of a full urodynamic analysis to use as a standard and the unreliability of some investigations of the lower urinary tract, outflow obstruction may not always be properly diagnosed.

In children with a sawtooth-shaped pattern both normal and abnormal IUT values were found. The extent to which this was caused by detrusor malfunction with or without outflow tract obstruction could not be assessed by this method.

In some patients who voided twice during the investigation flow rates were rather changeable. These observations militate against the existence of an anatomical obstruction. Theoretically, the results in a case of anatomical obstruction should remain relatively constant, whereas the findings in functional obstruction and dyssynergic bladder function are usually variable.

The sensitivity and specificity of the method could not be evaluated while the reliability of the other urological investigations used as a standard remains questionable.

Because of the relationship between upper urinary tract pathology and micturition disorders in children, we recommend an extension of standard radionuclide renography to include measurement of urine flow patterns and the index of urine transport as a method of screening lower urinary tract function. The examination takes longer, but the additional information obtained in one session (Fig. 3) compensates for this. It was concluded that a normal or biphasic voiding pattern and normal average and maximum IUT values are unlikely to be found in children with clinically significant urinary outflow tract pathology. A normal or biphasic voiding pattern, together with a moderately decreased IUT, is presumably due to a poorly contracting bladder or some hesitation during voiding. A "wait and see" approach is preferable to invasive urological investigations. A sawtooth-shaped pattern with or without normal IUT values requires careful analysis of the micturition history. A thorough urodynamic analysis should be undertaken. A low, flat urine flow pattern (obstructive curve), always accompanied by low average and maximum IUT values, requires an intensive (and usually invasive) urological analysis.

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Microbiology of the Urethral (Frequency and Dysuria) Syndrome. A Controlled Study with 5-year Review

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Summary—In a clinical and microbiological study of women with urinary frequency and dysuria (excluding those with bacterial cystitis), 41 patients were compared with 42 control subjects. No difference was found between patients and controls in the incidence of infection by *Chlamydia trachomatis* or other sexually transmitted organisms. The numbers of lactobacilli and other fastidious organisms in the urine of patients with either mild or severe symptoms were similar and did not differ from the numbers in the urine of control subjects. The numbers of leucocytes in urine were also similar in both patients and controls. Our findings support the view that the urethral syndrome is not caused by bacterial or chlamydial infection.

Recurrent dysuria and frequency of micturition are common symptoms in women, often related to sexual intercourse. Several studies have shown that in approximately half of the patients, the symptoms are due to bacterial cystitis caused by recognised urinary pathogens such as *Escherichia coli* (Murphy *et al.*, 1982; Kunin, 1987). The symptoms are often unexplained, however, and for these cases the term "urethral syndrome" has been used. The non-committal term "frequency and dysuria syndrome" is preferred by some, since there is usually no evidence of urethral disease (Medical Research Council, 1979). Some authorities believe there are several causes (Chattopadhyay, 1985) and many urologists believe that sphincter spasm (Kaplan *et al.*, 1980) and anatomical variations of the genitalia (O'Donnell, 1980) are of importance.

In recent years the belief that the urethral syndrome may sometimes be caused by infection has been revived (Stamm *et al.*, 1980) and the suggestion made that chlamydia may sometimes be responsible; reports by Maskell *et al.* (1979, 1983), Maskell and Read (1982) and Maskell (1986) suggested urethral infection by lactobacilli and other "fastidious" organisms, so called because they might not be detected by routine methods used for culturing *Escherichia coli* and other recognised causes of urinary infection. These findings were disputed by Brumfitt *et al.* (1981) and Hamilton Miller *et al.* (1986).

We have studied patients with the urethral syndrome and compared them with control subjects. The incidence of chlamydial and other sexually transmissible infections was recorded and the numbers of lactobacilli and other fastidious organisms in first-stream and mid-stream urine samples were enumerated. Leucocytes in urine specimens were also counted. Since it is possible that the syndrome has more than one cause, and since patients differ considerably in the duration and severity of symptoms, we compared the laboratory findings not only with the duration and severity of symptoms but also with the presence of visible abnormalities in the urethra.

Patients and Methods

The patients were women who consulted their family doctors because of recurrent frequency and dysuria not attributable to bacterial cystitis since urine culture for *Escherichia coli* and other recognised causes was negative during attacks. The patients, none of whom was pregnant, were referred to a consultant urologist (P.J.B.S.) at a special out-patient clinic during the year commencing 1 November 1982. The patients returned to the clinic at least once (and usually more often) during that year. None was being treated with antibiotics when

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they first attended, though a few did receive them subsequently. Their clinical progress was followed for further periods of between 4 and 5 years by questionnaires sent to their family doctors. Patients were subdivided on clinical grounds into 2 groups, A and B. Group A had mild symptoms requiring no treatment other than reassurance. Group B had more severe symptoms, often with visible changes in the urethra which required treatment by methods such as urethral dilatation. The subdivision into 2 groups was based on data-sheets on which clinical findings were scored: duration, severity and frequency of symptoms, painful micturition, urgency, incontinence, haematuria, dyspareunia.

The control subjects were healthy women who attended the family planning clinic at the hospital during the year commencing November 1982. Those with bacteriuria or with a history of frequency, dysuria or other symptoms of lower urinary tract infection were excluded, as were those with abnormal findings on vaginal examination. None was taking antibiotics. One or two control subjects were chosen each week, selecting those whose ages were similar to those of patients seen during the same period. Apart from this the selection was random.

Laboratory investigations

First-stream and mid-stream urine specimens were taken from patients attending the clinic and from control subjects. Some of the patients' specimens were taken during attacks of frequency and dysuria, but most were taken when they were asymptomatic. The specimens were kept at 4°C and processed within a few hours. Leucocytes in uncentrifuged urine were counted by an inverted microscopy technique (Rant and Shepherd, 1982) and Gram-stained smears of deposit were examined. Each specimen was inoculated by a quantitative standard loop method on CLED (cysteine lactose electrolyte-deficient medium, Mast Laboratories) and on two 5% horse-blood agar plates. The CLED plate was incubated in air at 37°C for 24 h. The blood agar plates were incubated at 37°C for 48 h, one with 5% CO_2 in air and the other anaerobically in hydrogen with 5% CO_2. The presence and numbers of lactobacilli, streptococci and corynebacteria were established by colony count and microscopy of the blood agar cultures.

The other specimens taken from patients and control subjects were cervical, vaginal and urethral swabs in transport medium (Amies, 1967) for microscopy for *Trichomonas vaginalis*, and microscopy and culture for *Gardnerella vaginalis* (Totten *et al.*, 1982), *Neisseria gonorrhoeae, Candida* spp. and *Chlamydia trachomatis*. Swabs in transport medium for chlamydia were processed within 24 hours in the Public Health Laboratory, Bristol (Richmond *et al.*, 1980).

Patients who had a recurrence of symptoms during the year of the investigation were asked to collect fore-stream and mid-stream urine specimens, to inoculate a MacConkey/CLED dip-slide culture (Oxoid) from the MSU and to send the dip-slide and the specimens to the laboratory on the same or following day. The dip-slides were incubated for *E. coli* and other causes of bacterial cystitis and the urines were cultured for fastidious organisms.

Results

Of the 52 patients who entered the investigation, 11 were subsequently withdrawn because other likely causes for their symptoms were found. These included 6 who were found on first attendance at the clinic to have bacterial cystitis, confirmed by urine culture, 4 who had severe atrophic changes in the urethra and 1 with interstitial cystitis. None had vaginitis.

The remaining 41 patients were considered to be suffering from the urethral syndrome. Their average age was 32 years (range 19–54); 15 patients were placed in Group A since their symptoms were relatively mild, had started recently, and were not considered to require treatment other than reassurance. The 26 patients in Group B complained of severe symptoms and most had suffered recurrent attacks for 2 or more years previously. Group B patients were investigated by cystoscopy and treated by urethral dilatation. The dilatation was repeated once in 6 patients and twice in 2. Eight patients were treated in addition by urethrolysis (Smith *et al.*, 1981) and 2 by urethrolysis and urethroplasty (Smith *et al.*, 1982). At subsequent attendances, 3 patients were found to have episodes of *E. coli* cystitis.

There were 42 control subjects with an average age of 26.2 years (range 19–32).

Isolation of sexually-transmissible organisms

The results were similar in both patients and control subjects (Table 1). None of the patients' swabs yielded chlamydia.

Fastidious organisms

There was no significant difference between the numbers of lactobacilli or other fastidious orga-

Table 1 Sexually Transmissible Organisms in Cervical, Urethral and Vaginal swabs

	Patients (n=41)	*Control subjects (n=42)*
Chlamydia trachomatis	0	2
Neisseria gonorrhoeae	0	0
Trichomonas vaginalis	0	0
Gardnerella vaginalis	2	2
Candida spp	2	4

nisms isolated from the urine of patients and control subjects (Table 2). Results from patients with severe symptoms and those only mildly affected were similar. As was to be expected, the viable counts in mid-stream urine were slightly less than in first-stream urine. Our findings therefore were similar to those of Brumfitt *et al.* (1981).

Pyuria

In a minority of patients, the urine contained an excess of leucocytes ($>10/mm^3$). This was seen in specimens taken while symptoms were manifest and also when the patients were symptom-free. However, the proportion with excess leucocytes did not differ significantly from the control subjects (Table 3).

Clinical findings

No urethral abnormalities were found in the 15 Group A patients, except for 1 with hymenal attachments at the external urethral meatus. These patients were not cystoscoped.

All 26 group B patients were examined by urethroscopy and cystoscopy; 15 (58%) were found to have distal urethral stenosis, 7 (27%) had trabeculation or inflammation of the bladder, and 4 of these patients had both abnormalities. Treatment by urethral dilatation, sometimes with urethrolysis and urethroplasty, was followed by relief of symptoms in 16 patients.

The results of the follow-up study are summarised in Table 4.

Table 2 Lactobacilli and Other Fastidious Organisms in First-stream and Mid-stream urine of 41 Patients and 42 Control Subjects Numbers with viable counts $>10^4$/ml

			First-stream		*Mid-stream*	
Subjects	*No of subjects*	*No of specimens*	*Lactobacilli alone or predominant (%)*	*Mixed fastidious organisms (including lactobacilli) (%)*	*Lactobacilli alone or predominant (%)*	*Mixed fastidious organisms (including lactobacilli) (%)*
Patients during symptoms	12	15	0	9 (60)	0	5 (33)
Patients at other times	41	92	11 (12)	50 (54)	10 (11)	42 (46)
Group A patients (mild symptoms)	15	31	4 (13)	14 (42)	4 (13)	11 (35)
Group B patients (severe symptoms)	26	76	7 (9)	45 (59)	6 (8)	36 (47)
Control subjects	42	42	8 (19)	25 (58)	3 (7)	21 (49)

Table 3 Pyuria in First-stream and Mid-stream Urine Specimens from Patients and Controls

	Leucocytes/mm³							
	First-stream				*Mid-stream*			
	Not recorded	*<10*	*10–100*	*>100*	*Not recorded*	*<10*	*10–100*	*>100*
Patients with symptoms (15 specimens from 12 patients)	1	9	3	2*	0	12	0	3*
Patients while symptom-free (92 specimens from 41 patients)	6	68	15	3	4	80	7	1
Control subjects (42 specimens)	2	23	13	4	1	33	7	1

* Two specimens were from patients with episodes of *E coli* cystitis (see text).

Table 4 Persistence of Symptoms during Period of 4–5 years Following the Investigation

	Group A (%) *(n=15)*	*Group B (%)* *(n=26)*
No improvement		
Symptoms persisted or recurred for whole period	4 (27)	10 (38)
Improvement		
No recurrence after 2 years	5 (33)	10 (38)
No recurrence	6 (40)	6 (23)

Discussion

When investigating a patient with dysuria and frequency of micturition it is obviously essential to exclude bacterial cystitis, since in the early stages of cystitis the urinary bacterial count may be within normal limits (Stamm *et al.*, 1980). It should be remembered, however, that some patients with the urethral syndrome may also on occasion suffer episodes of bacterial cystitis (O'Grady *et al.*, 1973). This was observed in 3 of our patients.

It is also important to exclude dysuria caused by sexually transmissible organisms. Stamm *et al.* (1980) obtained positive cultures for chlamydia in a significant number of young women with dysuria, many of whom were sexually promiscuous. Similar patients in Bristol attend the clinic for sexually transmitted diseases, with an incidence of chlamydia infection of approximately 19% (E. O. Caul, personal communication). The absence of chlamydia in our patients, as in those studied by O'Dowd *et al.* (1984), may be explained by their different background—namely women referred to a urologist by their family doctors.

The proposition that the urethral syndrome is due to urethral infection by lactobacilli and other fastidious bacteria, normal vaginal commensals, provoked controversy (Hamilton-Miller *et al.*, 1986; Maskell, 1986). These organisms, normal inhabitants of the vagina, are often found as contaminants in normal female urine. Thus it is important to determine whether they are consistently more numerous in urine from patients with the syndrome. Brumfitt *et al.* (1981) reported that lactobacilli were absent from suprapubic urine specimens from patients (as might be expected if they were causing urethral infection) and they found no significant difference between the numbers in mid-stream specimens from patients and control subjects. Papapetropoulou and Pappas (1987) found evidence to support Maskell's fastidious bacteria hypothesis, as did Barr *et al.* (1985) in a study of pregnant women. On the other hand, Seal and Cuthbert (1982) and Tait *et al.* (1985) agreed with Brumfitt *et al.* (1981) and did not support the hypothesis. Our findings also do not support the hypothesis, since lactobacilli and other fastidious bacteria were not more numerous in our patients' urine when compared with that of our control subjects. This negative conclusion was strengthened by the similar results of urine culture in patients with mild and with severe symptoms.

Maskell's suggestion that the urethral syndrome may be caused by lactobacilli, or other commensals, has been thought by some to be unlikely in view of the very slight pathogenic activity of the organisms. However, instances may be cited of other infections caused by normally non-pathogenic organisms when they are introduced into tissues where they would not normally exist, or when they invade already damaged tissues. Thus there may be no absolute reason why commensal bacteria could not infect urethral tissue damaged, for example, during sexual intercourse. However, our results do not support the suggestion.

The similarity of the leucocyte counts in the urine of our patients and control subjects was in marked contrast to the findings in bacterial cystitis, when very high counts are common (Murphy *et al.*, 1982; Kunin, 1987). This provides further evidence against the view that the urethral syndrome is caused by bacterial infection.

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Relationship between Detrusor Pressure and Urinary Flow Rate in Males with an Intraurethral Prostatic Spiral

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Summary—Six patients with acute urinary retention and 2 with prostatic obstruction and urge incontinence were treated with an intraurethral prostatic spiral and underwent pressure-flow studies 51 days (median) later.

Evaluation of pressure-flow parameters and pressure-flow plots by different methods gave conflicting results regarding the presence of infravesical obstruction; 6 patients showed no voiding symptoms and in 2 patients only moderate irritative symptoms remained.

The spiral allowed unobstructed voiding and is a good alternative to an indwelling urethral catheter. We recommend insertion of a spiral in patients with urinary retention if the waiting period for TURP is long or if the patient is unfit for surgery.

The intraprostatic spiral, which consists of a metal coil, was first described by Fabian (1980) and has been used in the treatment of patients with infravesical prostatic obstruction (BPH) (Fabian, 1980, 1984; Fabricius *et al.*, 1983; Flier and Seppelt, 1987). In these studies the spiral was inserted endoscopically with measurement of prostatic urethral length and visual positioning of the spiral, a procedure that was found to be very laborious.

A Danish gold-plated spiral has since been developed with a detachable device allowing transurethral insertion under surface analgesia with lignocaine jelly (Prostakath, Copenhagen, Denmark). Transabdominal ultrasonic scanning was used to measure the length of the prostatic urethra and to control the position of the spiral (Fig. 1). A series of 41 consecutive patients with acute or chronic urinary retention due to BPH received an intraprostatic spiral. Follow-up 3 months later revealed satisfactory voiding in the majority of patients, whose flow rates were comparable with those found in healthy men of the same age group (Nordling *et al.*, 1988).

The aim of this study was to investigate the urodynamic effects of the spiral by means of pressure-flow studies.

Patients and Methods

The study group comprised 8 men (median age 73 years, range 59–86) with benign prostatic hypertrophy who had been treated with an intraprostatic spiral 27 to 101 days earlier (median 51). Six patients were treated with the spiral because of acute urinary retention (retention volumes 400–1500 ml, median 850). The catheterisation period prior to insertion of the spiral ranged from 1 to 45

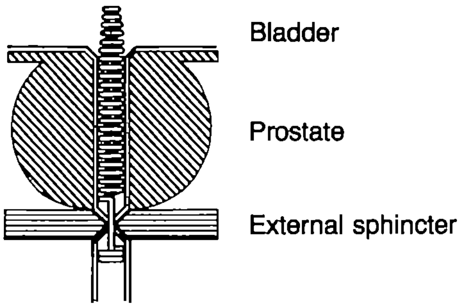

Fig. 1 A correctly positioned intraurethral prostatic spiral.

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days (median 7). Two patients presented with prostatic obstruction and urge incontinence; 1 of these underwent a pressure-flow study before insertion. The spirals had a body length of 45 to 75 mm, an outer diameter of 7 mm and an inner diameter of 6 mm. To facilitate abdominal ultrasound scanning the bladder was filled with 150 to 300 ml 0.01% chlorhexidine. With a balloon catheter *in situ*, abdominal ultrasonic scanning was performed to exclude tumour and stones. The prostatic urethral length was measured. A spiral 10 to 15 mm longer than this was chosen due to the posterior recurvation of the prostatic urethra in the sagittal plane and to ensure that the tip of the spiral was inside the bladder. The indwelling catheter was removed without emptying the bladder. After disinfection of the external urethral orifice with 0.02% chlorhexidine, the urethra was filled with 20 ml chlorhexidine-lignocaine jelly and the spiral was inserted under sterile conditions as for "normal" catheterisation. A urethral catheter no. 7 was used as a guide wire. Advancement of the spiral was controlled by abdominal ultrasonic scanning. When 10 to 15 mm of the spiral were seen inside the bladder an image of the complete body of the spiral was obtained. The length of the body measured should correspond to the length of the inserted spiral. Finally, the insertion catheter was removed.

At follow-up (median 51 days later), a voiding history was obtained. Uroflowmetry was performed and residual urine volume determined by transabdominal ultrasonic scanning. A 14 F catheter was placed in the anterior urethra and, by retrograde infusion, the bladder was filled with saline at body temperature until a strong desire to void was obtained. The intravesical pressure was measured via a suprapubically inserted 3.5 F catheter. Abdominal pressure was measured by means of a water-filled catheter covered with a finger cot placed in the rectum. Both catheters were connected through fluid-filled lines to external strain gauge transducers positioned at the level of the symphysis pubis. Detrusor pressure was derived electronically by subtracting the abdominal pressure from the intravesical pressure (Urodyn 5500, Dantec). The detrusor pressure at maximum flow rate (Pdet, Qmax), the detrusor opening pressure (Popen), the detrusor closure pressure (Po) and maximum flow rate (Qmax) were recorded. Po was defined as the detrusor pressure as flow ended. The minimum urethral resistance (MUR) (Pdet, Qmax/Qmax^2) was calculated. A plot of corresponding values of detrusor pressure and flow rate was made. According to Abrams and Griffiths (1979), plots with a mean slope <2 cm H_2O/ml/s and with detrusor pressure as flow ended <40 cm H_2O were classified as unobstructed (pattern C). Plots with a mean slope >2 cm H_2O/ml/s were classified as obstructed, (pattern B) and those with a mean slope <2 cm H_2O/ml/s but detrusor pressure at the end of the voiding >40 cm H_2O were classified as obstructed (pattern A). The pressure-flow plots and the nomogram are based on the concept of "urethral resistance relation", which describes graphically the relation between pressure and flow during voiding in order to define the lowest resistance supposed to represent the totally relaxed or passive bladder outlet. This concept places the flow-controlling zone in the proximal urethra (Griffiths, 1973, 1980).

Results

Six patients were without voiding symptoms and satisfied with the spiral. The pressure-flow parameters, residual urine volume and MUR for these patients are shown in Table 1. Coolsaet and Blok (1986) proposed the MUR$=0.5$ cm $H_2O/s^2/ml^{-2}$ as a threshold value for obstruction. In all 6 patients the MUR was below this value.

The evaluation of the Pdet, Qmax by the nomogram constructed by Abrams and Griffiths (1979) showed 1 patient with obstructed micturition, while the others were equivocal (Fig. 2).

Analysis of the plot of the entire micturition, by assessment of detrusor pressure at the end of voiding and the mean slope (Abrams and Griffiths, 1979), showed that 1 patient had obstructed pattern A, 2 had obstructed pattern B and 3 had unobstructed pattern C (Fig. 3). Blaivas and Rocha (1985) defined obstruction urodynamically either as a Qmax <12 ml/s with a Pdet, Qmax >45 cm H_2O or as a Qmax >15 ml/s with a Pdet, Qmax >75 cm H_2O. Using these definitions, the same 3 patients were found to have infravesical obstruction and the others unobstructed voiding.

Table 1 Pressure-flow Parameters in 6 Patients without Voiding Symptoms after Insertion of the Spiral

	Median	*Range*
Pdet, Qmax (cm H_2O)	46	25–77
Popen (cm H_2O)	28	20–52
Pclosure (cm H_2O)	18	10–65
Maximal flow rate (ml/s)	12	7.3–20.2
Residual urine (ml)	95	10–305
MUR (cm $H_2O/s^2/ml^{-2}$)	0.33	0.19–0.49

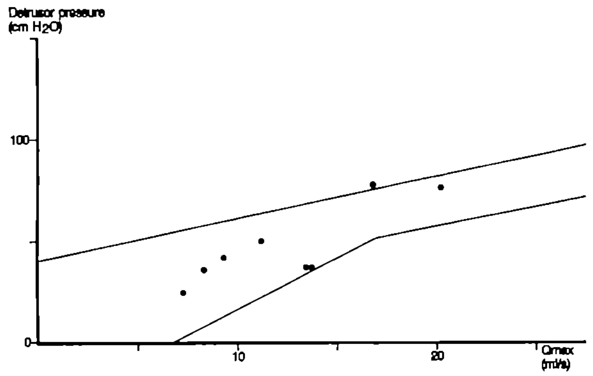

Fig. 2 Values of detrusor pressure at maximal flow rate in 8 patients with an intraurethral spiral.

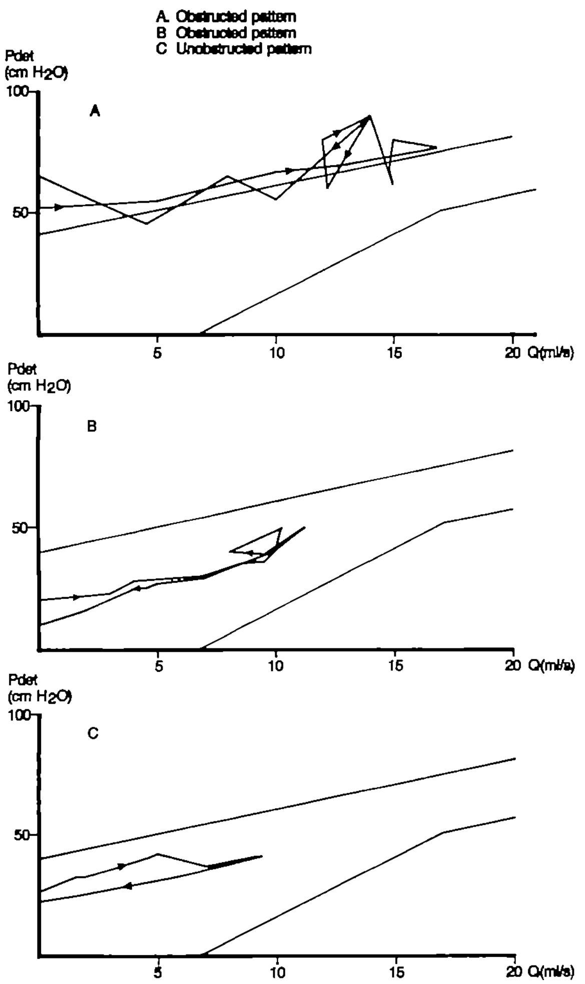

Fig. 3 Pressure-flow plots showing (A) obstructed pattern A, (B) obstructed pattern B and (C) unobstructed pattern C evaluated by the method of Abrams and Griffiths (1979)

It was not possible for us to analyse our data by the method of Schäfer (1985). However, Schäfer has reported that in normal unobstructed voiding, the values of the minimum pressure during flow and the theoretical effective cross-sectional area of the flow-controlling zone are <25 cm H_2O and >7 mm^2 respectively. In only 1 of the 6 patients without voiding symptoms was this pressure above 25 cm H_2O. In the "passive urethral resistance relation", elaborated by Schäfer (1985), the urethral opening pressure is an important parameter. However, using the computerised approach, the minimum urethral opening pressure is generally defined as the lowest relative detrusor pressure to occur during actual voiding. In 7 of our 8 patients this pressure corresponded with the closure pressure, *i.e.* detrusor pressure when the flow ended. This pressure was not exactly the same as the computerised minimum opening pressure.

In 2 patients the obstructive voiding symptoms disappeared, but moderate irritative symptoms such as frequency and urgency remained. The pressure-flow parameters, residual urine volume and MUR are shown in Table 2. Assessment of the Pdet, Qmax in the pressure-flow plot showed borderline obstruction in both patients. According to the definition of Blaivas and Rocha (1985), both patients had unobstructed voiding. The calculated mean slope of the entire pressure-flow plot showed obstructed pattern B in one and obstructed pattern A in the other. MUR was 0.52 and 0.20 cm $H_2O/s^2/ml^{-2}$ respectively. Both patients had normal minimum pressure during flow.

Table 3 and Figure 4 show the different parameters both before and after insertion of the spiral in a single patient.

Discussion

Transurethral prostatectomy (TURP) is the treat-

Table 2 Pressure-flow Parameters in 2 Patients with Persistent Moderate Frequency and Urgency after Insertion of the Spiral

	Patient	
	A	*B*
Pdet Qmax (cm H_2O)	36	37
Popen (cm H_2O)	28	30
Pclosure (cm H_2O)	12	11
Maximal flow rate (ml/s)	8.3	13.6
Residual urine (ml)	40	30
MUR (cm $H_2O/s^2/ml^{-2}$)	0.52	0.20

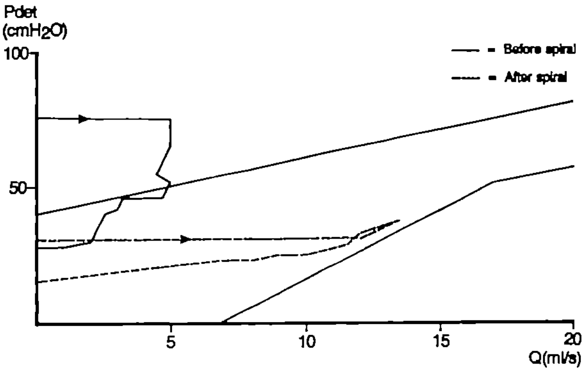

Fig. 4 Pressure-flow in 1 patient before and after insertion of the spiral.

ment of choice for infravesical obstruction due to benign prostatic hypertrophy (BPH). Nordling *et al.* (1988b) reported that the treatment of patients with acute or chronic urinary retention due to BPH with an intraurethral prostatic spiral showed subjective satisfactory voiding in most cases, although the long-term results are not known. To date, it has not been the intention that insertion of a spiral should replace TURP, but while awaiting operation (sometimes for 3 months or more) it could be advisable to insert a spiral in order to relieve voiding symptoms or to replace an indwelling catheter. Thus we found it timely to investigate the urodynamic effects of the spiral.

Interpretation of pressure-flow measurements by different methods gave conflicting results regarding the presence of normal or obstructed voiding. In only 1 patient was the MUR >0.5. MUR is based on hydrodynamic principles, however, which assume flow through a rigid tube and the existence of a flow-controlling zone in the distal urethra. However, the urethra is distensible and the flow-controlling zone is situated in the region of the pelvic floor (Griffiths, 1973, 1980; Schäfer, 1985). As a result, evaluation by MUR probably fails to distinguish between obstructed and normal voiding.

Table 3 Pressure-flow Parameters in 1 Patient before and after Insertion of the Spiral. After Insertion the Patient had no Voiding Symptoms

	Before	*After*
Pdet Qmax (cm H_2O)	76	37
Popen (cm H_2O)	76	31
Pclosure (cm H_2O)	20	15
Maximal flow rate (ml/s)	5	13 5
Residual urine (ml)	50	10
Mean slope (cm $H_2O/ml/s^{-1}$)	15	1 7
MUR (cm $H_2O/s^2/ml^{-2}$)	3.04	0.20

In 1 patient the minimum pressure during flow was greater than 25 cm H_2O and according to Schäfer (1985), this could signify obstruction. However, the inner cross-sectional area of the spiral of about 29 mm^2 is far beyond 7 mm^2 as the lower limit in unobstructed voiding. Theoretically, therefore, the spirals cannot be the flow-limiting factor. The clinical benefit to be obtained by the use of Schäfer's method in evaluating patients with prostatism has yet to be determined.

Evaluation of the pressure-flow studies by the methods of Abrams and Griffiths (1979) and Blaivas and Rocha (1985) agreed in 7 of 8 patients.

In a prospective study, the urodynamic findings were "blinded" prior to surgery and compared with the subjective outcome of surgery. Evaluation by the nomogram of Abrams and Griffiths (1979) proved useful as a predictor of the symptomatic outcome in patients with prostatism (Jensen *et al.*, 1988). The main goal of any therapy for BPH should be removal of the symptom complex of prostatism. In this study, insertion of the spirals removed the obstructive voiding symptoms in all 8 patients but moderate irritative symptoms remained in 2. This contrasts with the evaluation by the method of Abrams and Griffiths (1979), where 4 patients were found to have infravesical obstruction.

The pressure-flow studies in 1 patient before and after insertion of the spiral demonstrated clearly the conversion from obstructed to unobstructed micturition.

Urodynamic evaluation in cases with high Pdet, Qmax and low Qmax and with low Pdet, Qmax and high Qmax allows a reliable assessment of the presence of infravesical obstruction. In all other cases the urodynamic evaluation cannot reliably distinguish between obstructed and unobstructed micturition.

The size of the spiral seems sufficient to allow unobstructed voiding and is a good alternative to an indwelling urethral catheter. We recommend insertion of a spiral in patients with urinary retention if the waiting period for TURP is prolonged or the patient is unfit for surgery.

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Long-term Assessment of 107 Patients Undergoing Bladder Neck Incision

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Summary—The notes of 134 consecutive patients undergoing bladder neck incision (BNI) were analysed retrospectively. Details of pre-operative symptoms and the short-term results of the operation were studied, as well as the need for reoperation. Long-term results of the operation were not available in 100 patients and a questionnaire was sent to them asking for details of their present symptoms. This produced results on the long-term follow-up of 107 patients with a mean follow-up of 31 months (range 18–48); 86% of patients showed an improvement in symptoms in the short term whilst 68% maintained a subjective improvement in symptoms in the long term. Further surgery was required in 18 patients (13%). Possible reasons for this are discussed.

Bladder neck incision is an alternative operation to transurethral resection of the prostate (TURP) for patients with outflow tract obstruction and a small prostate gland which appears to be non-occlusive endoscopically (Edwards and Powell, 1982). Reports have been published on the results of BNI (Turner-Warwick *et al.*, 1973; Edwards and Powell, 1982; Moisey *et al.*, 1982; Delaere *et al.*, 1983; Christensen *et al.*, 1985; Edwards *et al.*, 1985; Orandi, 1985; Hellstrom, 1986; Nielsen, 1988). However, although the follow-up in some of these studies was quite long, the patient's symptoms were assessed only in the short term, *i.e.* up to 3 months after operation. We have performed this operation regularly in Eastbourne since 1983 and have studied the long-term symptomatic improvement.

Patients and Methods

The study involved analysing the notes of 134 consecutive patients who had undergone BNI from late 1983 to 1986. This provided details of pre-operative symptoms and symptoms at out-patient follow-up at 6 weeks. The long-term results were determined either from the notes, when the patient had been seen recently as an out-patient, or by a postal questionnaire which asked for details concerning urinary stream and frequency. Of 100 questionnaires posted, 78 were returned. Questionnaires were not sent to those patients known to have undergone a further procedure, unless it was a BNI; 10 patients were known to have died and their long-term results could not be evaluated. No deaths were related to surgery.

The mean age was 66 years (range 36–94). Presenting symptoms are shown in Table I. All patients were assessed pre-operatively by measurement of haemoglobin, blood urea and MSU, and by intravenous urography. Flow rates had not been performed routinely on these patients pre-operatively and so a flow rate was not performed as part of this long-term follow-up. The decision to perform a BNI rather than a TURP was taken by the surgeon at the time of endoscopy, if the appearance was that of a non-occlusive prostate but an obstructive bladder neck. BNI was performed unilaterally in all cases at 7 o'clock, incising from

Table 1 Mode of Presentation in 134 Patients

Presentation	*No.*	*%*
Acute retention	19	14
Chronic retention	10	8
Prostatism	105	78

Read at the 44th Meeting of the British Association of Urological Surgeons in Buxton, June 1988 the right ureteric orifice to the verumontanum through all layers. A quarter of the patients also had an endoscopic biopsy of the prostate performed at the same time. This was taken from the deep layers of the gland, adjacent to the incision in the bladder neck. Post-operatively a whistle tip catheter or an irrigation catheter was left *in situ* for 2 days.

Results

At out-patient follow-up, 6 weeks after the original operation, 133 of 134 patients attended. The results are shown in Table 2. The 3 patients undergoing a TURP at this stage did so for retention after their BNI.

The long-term results, as obtained by either questionnaire (78 patients) or by analysis of recent hospital notes (29 patients), are shown in Table 3. The 15 patients who underwent a further procedure included 3 who were eventually supplied with a permanent indwelling catheter for unrelated reasons, none being under the care of a urologist at that time. The remaining 12 patients underwent a TURP; if they are combined with the 2 patients undergoing a TURP who subsequently died and the 4 patients who underwent a second BNI, a reoperation rate of 13% is achieved. Of the 14 patients undergoing a subsequent TURP, the mean time after BNI was 18 months (range 1–43).

It is interesting to note that histology revealed malignancy in 4 of the subsequent TURP specimens (29%). However, none of the patients proceeding to a TURP was amongst those who had had an endoscopic biopsy. None of the biopsies showed evidence of malignancy.

Table 2 Short-term Follow-up in 133 Patients

	No	%
Better	116	86
No better	14	10
TURP	3	2

Table 3 Long-term Follow-up* in 107 Patients

	No.	%
Better	73	68
Same	13	12
Worse	6	6
Further procedures	15	14

*Mean 31 months (range 18–48).

Discussion

The short-term results of BNI (specifically symptomatic improvement) are well documented and show it to be a successful procedure, although only a few studies have included a large number of patients. Edwards and Powell (1982), Moisey *et al.* (1982), Delaere *et al.* (1983), Hellstrom (1986) and Nielsen (1988) all studied less than 50 patients but produced results showing 80 to 90% symptomatic improvement in the short term. However, larger series by Turner-Warwick *et al.* (1973) (70 patients), Orandi (1985) (646 patients), Edwards *et al.* (1985) (312 patients) and Christensen (1985) (131 patients) all produced similar results, with an improvement in symptoms in 80 to 90% of patients 3 months post-operatively. In our series, 86% of patients reported an improvement in symptoms 6 weeks after the procedure.

Our long-term results, 18 to 48 months (mean 31) after operation, showed 68% of patients with symptomatic improvement; 18% remained unchanged or became worse. The only study reporting long-term follow-up of patients underoing TURP is by Malone *et al.* (1988), in which 80% of patients showed an improvement in symptoms with a follow-up of 5 to 8 years. The 2 groups of patients in these 2 studies are not, however, directly comparable.

In the present series, 18 patients (13%) required a further procedure, 4 being a repeat BNI, with apparently good results. Our results span a follow-up period of 30 months (18–48 months after the original operation). If this is divided into 3 consecutive 10-month periods, the reoperation rates were 32, 20 and 5% on 34, 35 and 64 patients in each block. The lower reoperation rate in the most recent period may reflect a shorter follow-up, but the mean time to reoperation has been 18 months and all patients in the most recent period have been followed up for at least 18 months. We feel that this reflects our inexperience of the technique in the early months. The reoperation rates in other series has varied from 2% (Edwards *et al.* 1985) to 10% (Moisey *et al.*, 1982; Delaere *et al.*, 1983; Orandi, 1985).

Of the 14 patients requiring TURP, 4 (29%) were malignant. Only Orandi (1985) has studied the incidence of malignancy in TURP patients subsequent to a BNI and he reported an incidence of 11%. It is not known how many of the malignancies in our series, discovered at the subsequent TURP, would have been present at the time of the original BNI. Since these were unexpected malignancies and there was no clinical suspicion of this at the time of the BNI, it is unlikely that any specific treatment would have been instituted had the malignancy been discovered when the BNI had been performed. We would, however, stage the patient with at least a bone scan and serum acid phosphatase, as evidence of more distant tumour spread would clearly indicate a need for treatment. If it was shown to be truly an incidental malignancy, we feel the information remains of importance in order to follow the patient up more closely, and we advocate that all patients undergoing BNI have a biopsy at the time of operation.

The objective in this study was to assess symptomatic improvement after BNI. We are aware that retrograde ejaculation is a common occurrence after this operation but because we had decided to carry out the study using a postal questionnaire, it was not considered appropriate to assess this.

In conclusion, this series has shown the short-term success of BNI for bladder outlet obstruction to be comparable to that of other series. The long-term results show a sustained improvement in 68% of patients. We feel that this supports the view that BNI is a good operation in patients with a small non-occlusive prostate. We obtained slightly higher reoperation rates than those reported in other series and this may reflect our inexperience of the technique in early months. In patients undergoing a subsequent TURP, 29% had carcinoma of the prostate. We therefore feel that all patients undergoing a BNI should have a prostatic biopsy at the same time.

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Placenta Percreta Invading the Urinary Bladder

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Summary—The placenta, normally confined to the decidual lining of the uterine cavity, can in some circumstances invade the muscular wall of the uterus, a condition known as placenta accreta. Less common is placenta increta, in which placental cotyledons become intertwined with the muscular stroma of the uterus. Placenta percreta, in which the trophoblastic tissues penetrate the serosa of the uterus and may extend directly to adjacent structures, is even more rare and is potentially life-threatening.

There have been only 10 reports of direct invasion of placenta percreta into the urinary bladder. We review these cases and report 3 recent patients, one of whom was diagnosed pre-operatively by ultrasonography.

Few conditions in urological practice are as life-threatening as placenta percreta with direct invasion of the urinary bladder. Bacause patients with this condition may present with sudden gross haematuria, the urologist should be fully aware of this phenomenon, when the trophoblastic tissues penetrate the serosa of the uterus and may extend into neighbouring structures, often necessitating emergency gravid hysterectomy. Direct invasion of the placenta into the urinary bladder has been described on 10 previous occasions. In none of these patients was the diagnosis made pre-operatively. We report 3 recent cases, including the first to be diagnosed pre-operatively by ultrasonography. Of the 11 patients on whom data are available, a history of prior caesarian section was invariably present. Four of the women presented with gross haematuria. All who underwent prepartum ultrasound had a placenta praevia and those who underwent prepartum cystoscopy had abnormal findings. Nine patients each required more than 20 units of blood during surgery.

Adherent and invasive placentas can cause life-threatening haemorrhage during delivery. When a multiparous woman, who has undergone previous caesarian sections, is found to have a placenta praevia, invasive placenta must be included in the differential diagnosis. If gross haematuria is also present, bladder invasion by the placenta should be considered. Pre-operative diagnosis is possible with ultrasound and is helpful in patient management.

Case Reports

Case 1. C. C., a 33-year-old gravida 3 para 2 aborta 0 with 2 previous caesarian sections and a known placenta praevia, was seen at 34 weeks of pregnancy with a history of vaginal bleeding. On admission she was treated conservatively with bedrest and betamethasone to promote fetal lung maturity Serial amniocenteses revealed a mature lecithin:sphingomyelin ratio. After 2 weeks of expectant management she developed significant vaginal bleeding requiring emergency caesarian section. Through a high vertical hysterotomy a healthy female infant was delivered. The entire anterior surface of the lower uterine segment was replaced by extra-uterine placental tissue that extended laterally to the pelvic side walls and into the right iliac vessels, as well as superiorly into the intestinal mesentery. Frank invasion into the posterior wall of the bladder prevented easy dissection, and supracervical hysterectomy was rapidly performed. A cystotomy was created in the posterior wall of the bladder during hysterectomy. Massive haemorrhage ensued. Despite bilateral hypogastric artery ligation, attempts at haemostasis were unsuccessful and massive transfusion of blood and crystalloid was required. With the patient *in extremis* due to profound hypothermia and hypovolaemia, a median sternotomy was performed for open heart

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massage. The patient was placed on a cardiopulmonary bypass for rewarming. The posterior bladder wall was repaired in 2 layers. Haemostasis was obtained in an orderly fashion, included a left salpingo-oophorectomy and required a total of 115 units of blood. She was decerebrate on transfer to the intensive care unit and subsequently required tracheostomy and feeding gastrostomy. Over thge next 8 weeks her mental status improved and she was weaned from mechanical ventilation. She became alert and ambulatory and on the 84th post-operative day was transferred to a rehabilitation hospital for further care. She is presently living at home with her family.

Case 2 B. C., a 41-year-old gravida 6 para 4 aborta 1 with 3 previous caesarian sections and known marginal placenta praevia, presented at 36 weeks of pregnancy in premature labour. She was given tocolytic therapy and underwent amniocentesis that revealed a mature lecithin:sphingomyelin ratio. Her haematocrit of 25.8% was treated with 2 units of blood. Contractions ceased and she was taken to the operating theatre 3 days later for elective caesarian section. At exploration, her cervix and lower uterine segment were found to be densely adherent to the posterior wall of the bladder. A high vertical hysterotomy was made to deliver a healthy female infant.

The placenta was adherent to the uterus and attempts to separate it resulted in massive haemorrhage. A hysterectomy was undertaken to control the bleeding but this resulted in 2 large rents in the posterior bladder wall. An anterior cystotomy was made to facilitate dissection of the uterus and placenta from the bladder. During hospitalisation she required 21 units of blood. She did well post-operatively and was discharged 8 days later.

Case 3. R. P., a 31-year-old gravida 6 para 3 aborta 2 with 3 previous caesarian sections, was seen at another institution during her 20th week of pregnancy with a 2-day history of urinary frequency, gross haematuria and ultimately clot retention. After unsuccessful treatment for presumed haemorrhagic cystitis, she underwent a cystoscopic examination that revealed an area of erosive-looking mucosa on the posterior bladder wall. She was transferred to this hospital, where a haematocrit of 32.5% on admission dropped to 21 7% later that evening, and required the transfusion of 2 units of blood. Ultrasound examination revealed a placenta praevia percreta with invasion of the bladder Blood clots were also seen in the bladder. She was taken electively to the operating theatre for laparotomy by the urological and obstetric surgical services. After caesarian delivery of a non-viable male fetus, supracervical hysterectomy was accomplished. Massive haemorrhage was encountered from diffuse extra-uterine placental tissue A thick area of bleeding placental tissue, densely adherent to the posterior bladder wall, necessitated a partial cystectomy performed through an anterior cystotomy. Direct examination of the bladder mucosa revealed several small arteries pumping freely into the bladder cavity. The patient required 23 units of blood during surgery. She was discharged 18 days later. Histological examination of the specimen revealed trophoblastic invasion into the wall of the bladder and a loss of the transitional epithelium in that area.

Discussion

Placenta percreta with bladder invasion was first recorded within a placenta accreta series by Ochshorn *et al.* (1969). The following year there were 2 reports of multiparous women with previous caesarian sections who were admitted with gross haematuria and found at laparotomy to have placenta invading the bladder (Grabert *et al.*, 1970; Taefi *et al.*, 1970). Since then, 7 more reports of placental bladder invasion have been published (Silber *et al.*, 1973; Breen *et al.*, 1977; Collins *et al.*, 1978; Hutton *et al.*, 1983; Mathews, 1983; Trenton, 1984; Aho *et al.*, 1985). We add 3 more cases to this group.

Data were available for 11 of these patients (Table). All were multiparous and 10 were at least gravida 4. A history of prior caesarian sections was present in all, 9 of whom had undergone more than one. Four women were admitted with gross haematuria in the second trimester. Six patients were evaluated by prenatal ultrasound and all reported a placenta praevia. In 1 of our patients the diagnosis of placenta percreta invading bladder was suggested on sonographic evaluation. Prepartum cystoscopy was abnormal in each of the 4 patients who underwent the procedure. The posterior bladder wall was erythematous in 1, granular in 2 and had an exophytic lesion in the fourth. Transurethral biopsy of 1 lesion resulted in exsanguinating haemorrhage that required immediate gravid hysterectomy. All 9 patients in whom transfusion data were available required multiple transfusions, 6 of them receiving more than 20 units. Viability of the neonate correlated with gestational age; no infant of less than 25 weeks' gestation survived.

Abnormally adherent placentas can be life-threatening, leading to massive haemorrhage during attempts to dislodge and deliver them. When a placenta percreta with invasion of adjacent structures occurs, surgical removal is mandatory. A recent review of 97,799 consecutive obstetric cases reported placenta accreta in 24% of women with placenta praevia and 1 prior caesarian section. When more than 1 caesarian section had been performed, the presence of placenta praevia correlated with a 48% incidence of placenta accreta (Clark *et al.*, 1985). The association between

Table Comparison of the Thirteen Reported Cases of Placenta Percreta Invading the Urinary Bladder

Author	*Age (years)*	*Parity*	*Gestational age (weeks)*	*Prev c/s*	*Presenting symptoms*	*Diagnosis made pre-op*	*Transfusion (units)*	*Pre-op. cystoscopic findings*	*Pre-op. sonographic findings*	*Emergency laparotomy*	*Status of infant*
Ochshorn *et al.* (1969)	37	G6 P2	30	2	Premature rupture	No	N/R	N/R	N/R	No	Viable
Taefi *et al* (1970)	39	G8 P6	17	6	Haematuria	No	14	*	N/R	Yes	Non-viable
Grabert *et al* (1970)	35	G13 P8	23	4	Haematuria	No	N/R	†	N/R	Yes	Non-viable
Siber *et al* (1973)	29	G5 P4	20	3	Haematuria	No	46	‡	N/R	Yes	Non-viable
Breen *et al.* (1977)						No data reported					
Collins *et al* (1978)	31	G4 P3	40	3	Vaginal bleeding	No	22	N/R	N/R	No	Viable
Matthews (1983)	26	G4 P3	34	3	Suprapubic pain	No	10	N/R	Plac. prev	No	Viable
Hutton *et al.* (1983)						No data reported					
Trenton (1984)	37	G4 P2	37	1	Pre-eclampsia	No	4	N/R	Plac. prev.	No	Viable
Aho *et al.* (1985)	34	G5 P1	36	1	Abdominal pain	No	29	N/R	Plac. prev.	No	Viable
Present study (1987)	33	G3 P2	34	2	Vaginal bleeding	No	115	N/R	Plac prev.	Yes	Viable
(1987)	41	G6 P4	36	3	Premature labour	No	21	N/R	Plac. prev.	No	Viable
(1987)	31	G6 P3	20	3	Haematuria	Yes	23	§	Plac. prev. percreta	No	Non-viable

* First examination normal Second examination revealed a granular 0.5 × 0.5 cm lesion at the dome.
† Exophytic trigonal "growth" on posterior wall and trigone.
‡ First examination normal. Second examination revealed granular mucosa with one arterial bleeder.
§ First examination revealed minimal hyperaemia at trigone and erosive-looking mucosa on left posterior wall Second examination revealed an erythematous posterior wall with clot overlying the right ureteric orifice.
N/R = Not reported

adherent placentas and previous caesarian section, endometrial curettage and multigravity (Fox, 1972) supports the theory that previous endometrial insult predisposes to placenta accreta, increta and percreta. Placenta percreta has rarely been documented in the medical literature. Placenta accreta, increta and percreta are reported to have an incidence as low as 1 in 93,000 deliveries (Althabe and Althabe, 1963). Placenta percreta is thought to be due to a defect in the layers of the decidua basalis (Irving and Hertig, 1937; Kistner *et al*., 1952). It may carry with it the devastating complication of spontaneous uterine rupture during labour (Golden and Betson, 1959). In such cases, placenta percreta has been diagnosed on antepartum sonography only when massive intraperitoneal haemorrhage was found (Taylor *et al*., 1958; Sumawong *et al*., 1966). We report the first case of placenta percreta with bladder penetration in which the diagnosis was made pre-operatively in the absence of intraperitoneal bleeding.

With the reported correlation between adherent placentas and previous hysterotomy, the caesarian section rate may be related to an increasing frequency of placenta accreta, increta and percreta. When a multiparous woman who has undergone previous caesarian section is found to have a placenta praevia, the diagnosis of placenta accreta, increta and percreta should be entertained. Few of these patients have haematuria, but its presence should suggest the possibility of bladder invasion by the placenta. It is advisable to obtain informed consent for a possible gravid hysterectomy from all women at risk of adherent placentas. With some degree of suspicion by the clinician, the diagnosis may be made prior to surgical intervention.

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Glycine Irrigation and Urinary Oxalate Excretion

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Summary—The short-term effect of glycine supplementation on urinary oxalate excretion was studied. An intravenous infusion of 1 litre of a solution of 2.2% glycine, 1.5% glycine + 1% ethanol or 5% mannitol (control) was given on 13 occasions to 5 healthy volunteers. Glycine irrigation was used in 9 patients undergoing transurethral prostatic resection and the absorption of irrigant was measured volumetrically (range 0–2.7 l). The results suggest that glycine irrigation in transurethral prostatic surgery does not raise the urinary oxalate level in the early post-operative period.

Isotonic or slightly hypotonic solutions of glycine are widely used for bladder irrigation in transurethral prostatic resection (TURP). During this surgical procedure, absorption of irrigant through severed prostatic veins often results in the entry of glycine into the bloodstream (Alexander *et al.*, 1986). In recent years it has been acknowledged that the uptake of glycine can have potentially harmful metabolic sequelae. The detection of greatly increased urinary excretion of oxalate and glycolate in some patients following TURP led Fitzpatrick *et al.* (1981) to suggest that the absorption of irrigant containing glycine can lead to calcium oxalate renal lithiasis, especially if the urinary volume is allowed to fall. The aim of this study was to ascertain whether glycine uptake elevates the urinary oxalate level in the early post-operative period. We also examined the effect on oxalate excretion of adding ethanol to the irrigating solution; this was prompted by the recent development of a method for immediate detection of irrigant absorption that relies on marking of the irrigant with ethanol (Hahn, 1988).

Patients and Methods

Urinary oxalate concentration was measured by a spectrophotometric enzymatic procedure (normal range 0.2–0.5 mmol/24 h or 8–21 μmol/h) (Laker *et al.* 1980) in 2 groups of subjects.

Intravenous infusion of irrigating fluid, at a rate of 1 litre in 20 min, was performed in 5 fasting male volunteers (mean age 30 years). After voiding just prior to the infusion at 0800 h, the oxalate concentration was measured on urine collected during infusion and during a 2-h follow-up period. Thirteen infusions were given in random order on different occasions; the irrigants used were 5% mannitol (control), 2.2% glycine and 1.5% glycine + 1% ethanol.

The second group comprised 9 patients (mean age 71 years) undergoing TUR due to benign prostatic hypertrophy. In 1 patient who developed the TUR syndrome (Alexander *et al.*, 1986) the urinary oxalate excretion was followed for the first 16 h after completion of the resection; the remaining 8 patients were selected from a series of 50 to represent various degrees of irrigant absorption; in these patients careful volumetric measurements were made of the irrigating fluid balance and serum electrolytes over 10-min periods during resection (Hahn *et al.*, 1988), as well as urinary oxalate excretion during resection and the first 2 h post-operatively. The irrigating fluid used during resection was 2.2% glycine in water (n = 8) or 1.5% glycine + 1% ethanol (n = 1). Both irrigants are produced by Travenol, Bromma, Sweden.

Informed consent was given by all subjects and both research programmes were approved by the Ethics Committee of Huddinge University Hospital.

Results

Oxalate excretion, measured in connection with the intravenous infusions of irrigating fluids containing

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mannitol, glycine and glycine+ethanol, is presented in Table 1. The volume of irrigant absorbed, the total change in serum sodium concentration and the post-operative urinary oxalate excretion in 8 patients undergoing transurethral prostatic resection are shown in Table 2; the oxalate concentration measured on the irrigant returns during resection in these cases was invariably too low for detection by the method used. The patient who developed a severe TURP reaction had hypotension, severe confusion and stupor, and recorded a decrease of 27 mmol/l in serum sodium concentration during resection; the post-operative fluid balance and urinary creatinine and oxalate excretion are shown in Table 3.

Table 1 Urinary Oxalate Excretion 0–2 h after Intravenous Infusion of 1 litre of Various Irrigating Fluids (normal range 8–21 μmol/h)

Volunteer no	*5% mannitol*	*2.2% glycine*	*1.5% glycine + 1% ethanol*
1	10	14	
2	19	4	15
3	23	12	18
4	10	10	15
5	8		12
Mean	14	10	15

Discussion

Studies in which patients with and without renal lithiasis were compared indicate a higher mean oxalate excretion in the former group (Menon and Mahle, 1982); this points to the pathophysiological significance of elevated oxalate excretion. About 40% of the oxalate appearing in the urine is formed as a result of glyoxylate metabolism. In rats only 0.5% of an excess supply of glycine was converted to oxalate (Richardson, 1973), but being readily converted to glyoxylate, glycine is regarded as an important oxalate precursor (Menon and Mahle, 1982). In a study of 34 patients undergoing TURP, Fitzpatrick *et al.* (1981) found 3 cases with hyponatraemia in the morning following operation; in all of these the urinary excretion of oxalate was

Table 2 Fluid Absorption and Urinary Oxalate Excretion in 8 Patients Undergoing TURP

Patient no	*Pattern of irrigant absorption*	*Volume of irrigant absorbed (l)*	*Total change in S-Na during TUR (mmol/l)*	*Volumetric fluid balance 0–2 h after TUR (l)**	*Oxalate excretion (μmol/h)*
1		0	0	−0.25	30
2	Mid-TUR	0.13	0	+0.05	n.d.
3	Scattered	0.22	0	−0.32	34
4	Whole TUR	0.99	−8	−0.25	28
5	End of TUR	1.09	−13	−0.25	n.d
6	End of TUR	1.11	−13	−0.34	32
7†	Whole TUR	1.91	−8	Not measured	n.d.
8	Whole TUR	2.70	−16	+0.62	29

* − denotes recovery of fluid in excess of the input (with correction for blood loss).
+ denotes recovery of fluid smaller than the input (with correction for blood loss).
n.d. not detectable.
† irrigating fluid was 1.5% glycine + 1% ethanol.

Table 3 Irrigating Fluid Balance and Urinary Excretion of Creatinine and Oxalate after TURP Syndrome in 1 Patient

Period after TUR (h)	*Returned irrigant volume (l)*	*Volumetric fluid balance (l)**	*Creatinine excretion (mmol/h)*	*Urinary oxalate concentration (mmol/l)*	*Oxalate excretion (μmol/h)*
0–0.5	3.7	−0.6	0.71	n.d.	n.d.
0.5–2	4.3	−1.2	0.54	0.02	55
2–5	4.3	−1.2	0.57	0.01	14
5–16	4.4	−1.3	0.50	0.03	13

* − denotes recovery of fluid in excess of the irrigant input (with correction for blood loss)
n.d. not detectable; <0.01 mmol/l.

considerably elevated. Proof that the increased urinary oxalate arose from absorbed glycine was indicated by the fact that the excretion of glycolate, an intermediate in the metabolism of glyoxylate to oxalate, was also raised in these patients. Malone *et al.* (1986) found transient hyperoxaluria in 2 of 15 patients after TURP. However, this did not occur in any of the 8 patients who had a moderate degree of hyponatraemia (129–135 mmol/l). Furthermore, 1 patient who developed the TURP syndrome with profound hyponatraemia showed a normal urinary excretion of oxalate.

In all of the subjects included in this study, urinary oxalate excretion was normal during the first 2 h after receiving glycine + ethanol and isotonic glycine. Since mannitol is not metabolised, infusions of isotonic mannitol served as controls; the amounts of oxalate excreted after infusion of mannitol were similar to those recorded when glycine was supplied (Table 1). Thus the results of this infusion experiment suggest that bladder irrigation, using glycine or glycine-ethanol solutions, does not produce hyperoxaluria in the immediate post-operative period. However, for ethical reasons no more than 1 litre of irrigant was infused in the volunteer subjects on a single occasion. In the clinical situation, larger amounts of irrigant can be taken up (Alexander *et al.*, 1986). Accordingly, oxalate excretion was determined after a series of transurethral prostatic resections, where the precise irrigant absorption had been measured volumetrically. It should be noted that the post-operative bladder irrigation practised at this hospital diluted the urine to a volume of 5 to 6 litres during the 2-h follow-up period. The data presented in Table 2 are therefore based on quite low oxalate concentrations, which tend to be slightly overestimated by the method used (Laker *et al.*, 1980). However, to judge from the wide range of irrigant volumes absorbed during the resections, there is clearly no correlation between oxalate excretion and glycine uptake (Table 2). Finally, during post-operative follow-up of the patient experiencing a severe resection reaction, low oxalate concentrations were measured and the pattern of oxalate excretion level was not indicative of hyperoxaluria. Creatinine excretion demonstrated that there was no anuria; indeed, the volumetric fluid balance even indicated vigorous diuresis (Table 3).

In conclusion, the findings suggest that no correlation exists between glycine absorption and urinary oxalate excretion. Accordingly, forced diuresis immediately after transurethral prostatic procedures would seem not to be indicated solely because glycine solution has been used for bladder irrigation.

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Oestrogen Dosage in Prostatic Cancer: the Threshold Effect?

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Summary—We present the results of a prospective randomised trial of Estradurin, a long-acting oestrogen preparation (polyoestradiol phosphate), 160 mg per month, compared with bilateral orchiectomy in patients with advanced prostatic carcinoma (T3M1; T4MO/M1). The dose was lower than that usually recommended to induce a consistent fall in serial plasma testosterone levels to within the castrate range. Most patients treated with oestrogen showed an initial clinical and biochemical response equal to that obtained for patients undergoing orchiectomy. The inevitable relapse in hormone sensitivity sometimes occurred very soon after the start of oestrogen treatment. Many patients had poorly suppressed plasma testosterone expressed as a mean of monthly serial measurements, but then responded to secondary orchiectomy. These data only suggest that, in the treatment of hormone-sensitive prostatic carcinoma, it may be necessary to reduce plasma testosterone to midway between castrate and normal ranges. The data support the theory that response to androgen withdrawal is qualitative rather than quantative. The effective dose of oestrogen may therefore be reduced and the risk of thrombo-embolic complications minimised.

Orchiectomy will give temporary remission in over 80% of patients with advanced prostatic cancer (Walsh, 1975; Scott *et al.*, 1980; Trachtenberg, 1987). Oral oestrogens, in a dose sufficient to suppress plasma testosterone to castrate levels, will also control disease but may introduce the potentially fatal side effects of thrombo-embolism and salt and water retention (Byar, 1973). Unfortunately, the standard dose of the preparation commonly used in Britain and the USA, diethylstilboestrol (DES) 3 mg/day, may cause severe cardiovascular complications in 20% of patients (Leuprolide Study Group, 1984) and yet both disease control and thrombogenesis are apparently dose-responsive. The VACURG trials have indicated that DES (1 mg/day) gives adequate control of disease with minimal cardio-vascular complications (Kent *et al.*, 1973; Blackard, 1975). Urologists have been reluctant to use this dose as the plasma testosterone level may not fall to within the castrate range (Kent *et al.*, 1973; Shearer *et al.*, 1973) and it is therefore assumed that the therapeutic effect may be inadequate. However, there is experimental evidence that there may be a threshold level of plasma testosterone which is above the castrate range and below which the tumour can be controlled (Trachtenberg, 1985).

Nevertheless, interest in oestrogen therapy as an alternative to orchiectomy has waned, particularly with the development of agents to achieve medical castration such as LHRH super analogues and a range of androgen antagonists (Smith, 1987; Waxman, 1987). However, these are extremely expensive and their routine use is hard to justify (Gillatt, 1988). Thus a review of oestrogens as a means of treating prostatic cancer is warranted.

In this study, low dose oestrogen therapy and surgical orchiectomy were compared in patients with advanced prostatic carcinoma. The data presented identify a level of suppression of plasma testosterone and luteinising hormone critical to the control of hormone-sensitive prostatic cancer.

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Patients and Methods

A group of 117 patients with advanced prostatic carcinoma was randomised either to undergo bilateral subcapsular orchiectomy (n = 56) or to receive oestrogen in the form of a parenteral depot preparation—polyestradiol phosphate (Estradurin—Leo Ab, Helsingborg, Sweden) 160 mg im per month (n = 61) (Jonsson, 1963). All patients had advanced symptomatic disease and progress could therefore be regularly assessed. Only 11 patients were without evidence of bone metastases (MO).

Patients on treatment with oestrogen who did not respond, or who relapsed early, underwent secondary orchiectomy (n = 32). Some achieved a second response before finally relapsing with the development of disease resistant to hormone manipulation. Ultimately, 4 treatment groups were defined: primary orchiectomy; Estradurin; Estradurin with response to secondary orchiectomy; Estradurin with no response to secondary orchiectomy. All patients who underwent secondary orchiectomy had previously received oestrogen treatment for at least 3 months.

Response to treatment

In patients with symptomatic skeletal metastases an attempt was made to quantitate the rate of improvement in bone pain. The period required for sustained reduction in dosage or discontinued use of analgesics was recorded. Serial skeletal radiology and isotope imaging (99 m Tc diphosphonate) were evaluated but, in general, they gave a less sensitive indication of response to treatment than clinical and biochemical assessments.

Response was often subjective in patients with symptomatic local disease, although improvement in ureteric obstruction could be detected objectively. Lymphoedema and lymphadenopathy were readily evaluated.

The biochemical response to treatment was signified by a fall in plasma acid and alkaline phosphatase (routine enzymatic assay), though not necessarily to within the normal range. Plasma alkaline phosphatase often showed a considerable elevation above pre-treatment levels before falling ("a flare") in response to treatment. The number of patients responding was expressed as a proportion of those capable of response. Patients were therefore included only if phosphatase levels increased from a normal pre-treatment level or if they were elevated initially. The patients with normal phosphatase levels throughout were excluded from these analyses.

Plasma testosterone and LH were measured before treatment and at regular intervals afterwards. Blood was taken between 1400 and 1600 h, just before the regular monthly dose of Estradurin was given. Laboratory measurements were as previously described (Bishop *et al.*, 1985). Pretreatment and mean (+SD) values of serial plasma hormone measurements on each patient are presented for discussion.

Patients were assessed for the development of thrombo-embolic complications and account taken of evidence of previous cardiovascular disease.

Results

Clinical response (Table 1)

The majority of patients treated with either Estradurin or primary orchiectomy showed at least a partial clinical response as demonstrated by a reduction in skeletal pain, diminishing symptoms of rapidly advancing local disease causing obstruction at the bladder neck, ureter and rectum, and by diminution of lymphadenopathy and lymphoedema. Thus Estradurin was at least temporily effective, even though the hormon dosage was insufficient to maintain a satisfactory response in some patients.

Table 1 Clinical Response

	Estradurin	*Primary orchiectomy*
Bone metastases		
%M1 Patients with skeletal pain	69 (n = 36)	57 (n = 25)
Maximal response achieved (%)	<1 month 58	44
	1–2 months 27	36
	>2 months 12	16
	No response	4
Local disease		
% Patients with obstruction	42 (n = 25)	34 (n = 18)
% Bladder outflow	84	72
Ureteric	8	17
Rectal	8	11
No response	28	11
(all requiring TUR prostate)		
Lymphatic		
% Patients with lymphoedema, lymphadenopathy	5	15
Response	100	100

Table 2 Plasma Biochemical Response

	Phosphatases							
	Estradurin 1° Ox				*Estradurin no response to 2° Ox*		*Estradurin: response to 2° Ox*	
	Alk	Acid	Alk.	Acid	Alk	Acid	Alk.	Acid
No.	25	28	42	33	14	12	13	9
% response	92	79	86	88	14	42	92	100

Ox. orchiectomy.

Biochemical response (Table 2)

Plasma phosphatases showed an initial response in the majority of patients whose clinical response to primary or secondary orchiectomy or to Estradurin alone was satisfactory. Patients who did not respond to secondary orchiectomy had a poor initial biochemical response to Estradurin.

Cardiovascular complications (Table 3)

More patients on treatment with Estradurin developed a cardiovascular complication than those undergoing orchiectomy, but there were fewer deaths in patients on hormone treatment. A past history of cardiovascular disease predisposed to recurrent thromboembolic problems for both forms of treatment.

Plasma hormone levels

There was wide individual and group variation in plasma testosterone levels before and on treatment with Estradurin (Fig. 1). Most patients had mean levels on treatment above the castrate range but below the lower limit of the normal range (8 nmol/l) (Fig. 2). Patients responding to secondary orchiectomy tended to have mean levels on hormonal treatment above 4 to 5 nmol/l and more than 30% of the pre-treatment testosterone level. Patients who did not respond to secondary orchiectomy had plasma testosterone levels similar to those of patients who had remained on Estradurin treatment and whose response had been regarded as satisfactory. Mean levels on treatment were generally below 4 nmol/l and less than 30% of pre-treatment values. Conventional oestrogen treatment (DES 3 mg/day) suppressed plasma testosterone to a much greater extent than Estradurin and to levels comparable with the group treated by orchiectomy (Fig. 2).

Plasma LH levels were suppressed in all groups (Fig. 3). The mean level in patients treated with Estradurin, but not undergoing secondary orchiectomy, were similar to those in patients treated with DES 3 mg/day. Patients who eventually underwent secondary orchiectomy had higher mean levels of LH.

Plasma oestradiol was elevated in all patients on hormonal treatment. There was no relationship with the fall in plasma testosterone, expressed as a percentage of the pre-treatment levels (Fig. 4).

Table 3 Cardiovascular Complications

	Estradurin *n*	*Primary orchiectomy* *n*
Total	61	56
Cardiovascular complications*	8 (13%)	4 (7%)
Cardiovascular complications and previous cardiovascular disease	3	4
Previous cardiovascular disease No complications on treatment	5	8

* Including deaths Deaths and cardiovascular complications occurred in different patients

Complications in patients on Estradurin treatment comprised deep vein thrombosis (1), acute ventricular failure and cardiac arrhythmia (2) and arterial embolus (1). Cardiovascular deaths (Estradurin 3, orchiectomy 4) were invariably from myocardial infarction.

Discussion

Estradurin 160 mg/month is a lower dose than that recommended by urologists in Europe who favour this form of oestrogen treatment (Haapiainen *et al.*, 1986; Henriksson *et al.*, 1986). Its inability consistently to suppress plasma testosterone to within the castrate range was evident. Nevertheless, this study has demonstrated that clinical and biochemical

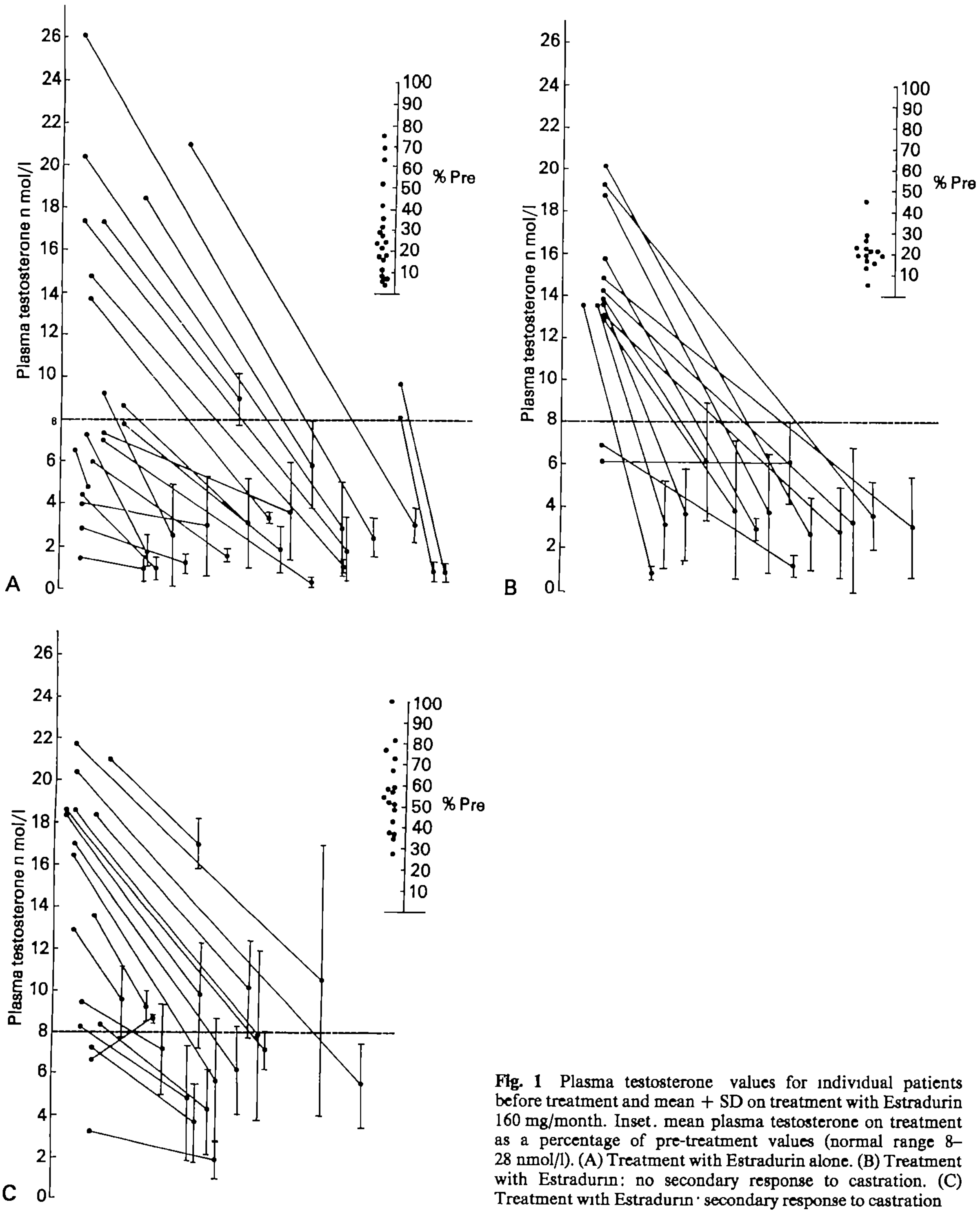

Fig. 1 Plasma testosterone values for individual patients before treatment and mean + SD on treatment with Estradurin 160 mg/month. Inset. mean plasma testosterone on treatment as a percentage of pre-treatment values (normal range 8–28 nmol/l). (A) Treatment with Estradurin alone. (B) Treatment with Estradurin: no secondary response to castration. (C) Treatment with Estradurin: secondary response to castration

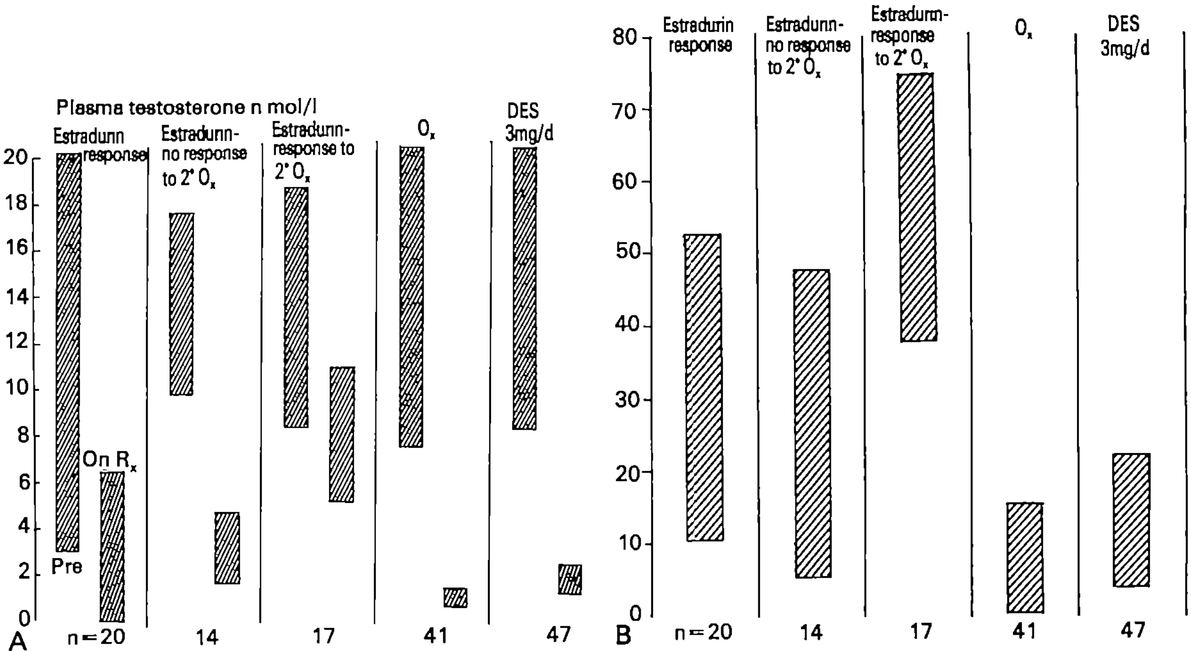

Fig. 2 Plasma testosterone on treatment. with Estradurin; primary or secondary orchiectomy (O_X); stilboestrol 3 mg/day. (A) Group values, mean + SD before and during treatment. (B) Mean plasma testosterone as a percentage of pre-treatment values

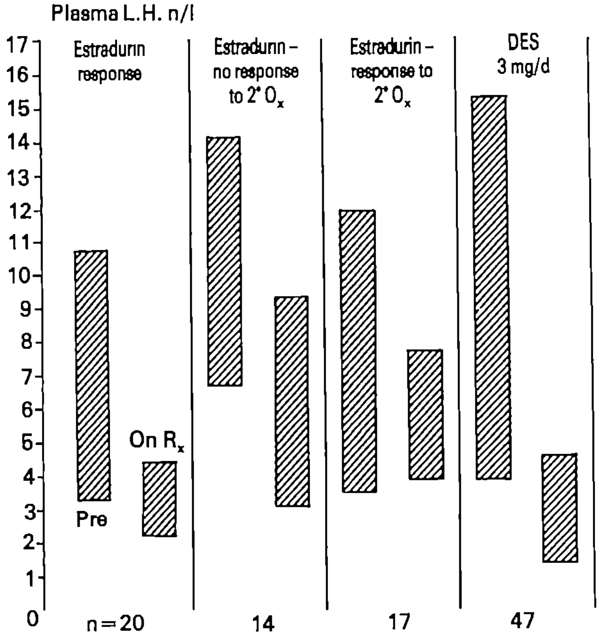

Fig. 3 Plasma LH: mean + SD before and during treatment (normal range 3–12 mu/l).

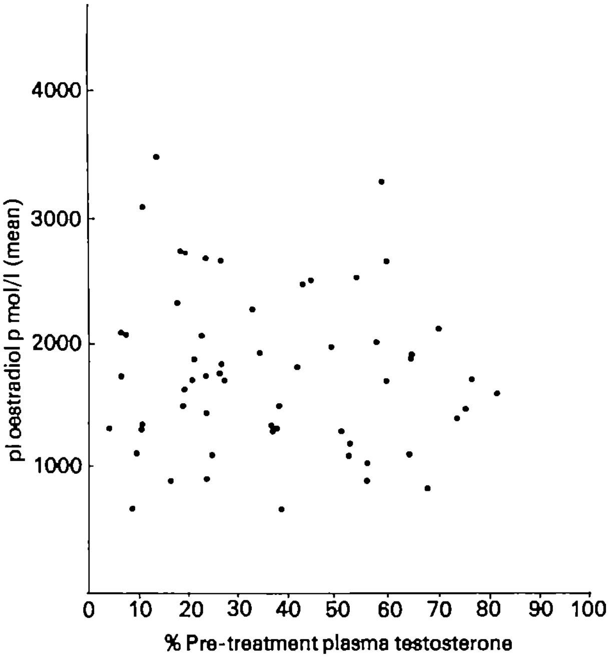

Fig. 4 Mean plasma oestradiol (normal range up to 220 nmol/l) versus mean plasma testosterone on treatment as percentage of pre-treatment values.

control of the tumour can still be achieved. The design of the trial, with provision for secondary orchiectomy and hence opportunity for a second chance of hormonal control, allowed an upper limit of plasma testosterone to be defined beyond which response was likely to be inadequate in extent and duration. In general, the dose of oestrogen which suppressed the mean of serial monthly plasma testosterone measurements to 30% of the pre-treatment levels and to below 4 nmol/l was adequate. It may be inferred that once these levels have been achieved, there is little to be gained by increasing the dose of oestrogen, even if the clinical and biochemical response is sub-standard, and it can be safely assumed that the tumour is truly resistant to hormonal manipulation. This is in accord with the dose threshold demonstrated in experiments with the transplantable Dunning prostate tumour in castrated rats (Trachtenberg, 1985). Estradurin, in a dose of 160 mg/month, had an equally variable effect on LH levels and they were not necessarily lowest where testosterone was maximally suppressed. An inverse proportion between plasma testosterone and LH on the one hand and oestradiol on the other might have been expected but could not be demonstrated in this study. However, oestrogens can suppress plasma androgen levels by a direct effect on testicular interstitial cells (Jones *et al.*, 1978). This effect might be more important than indirect suppression through feedback on the hypothalamo-pituitary—testicular axis and is not necessarily dose-responsive.

It is not surprising that thrombo-embolic complications occurred in a group of mainly elderly men with advanced malignancy. Hormone treatment may have contributed to morbidity, though the mortality was similar in patients treated with Estradurin and orchiectomy. The risk of complications was obviously less than for oestrogen therapy in conventional dosage (Henriksson *et al.*, 1986). This may have simply reflected the relatively low dose. It may also have derived from the use of a parenteral preparation, so avoiding the synthesis of certain thrombogenic proteins by "first-pass" liver metabolism which can be demonstrated with oral oestrogen preparations (Holst *et al.*, 1983; Daehlin *et al.*, 1986; Stege *et al.*, 1988).

The present study has demonstrated that most patients will respond to a low dose of oestrogen. Careful monitoring of the plasma testosterone is required to ensure that suppression is adequate so that the response will be optimal. Satisfactory clinical control of prostate cancer can be achieved by other regimes aimed at minimising the total dose of oestrogen. For example, it has been demonstrated that intermittent therapy can be effective (Vahlensieck *et al.*, 1985; Klotz *et al.*, 1986) and is unlikely to cause life-threatening thrombo-embolic complications. It is possible that the tendency to develop such complications can be monitored and forecast from levels of certain serum markers of haemostatic function (Henricksson *et al.*, 1986). The dose of oestrogen can then be determined and adjusted for any individual patient with reference to his own particular threshold of plasma testosterone. With these improvements, oestrogen therapy can then be considered as a third option which compares favourably with costly LHRH analogues and surgical orchiectomy.

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A Search for Infectious Agents in Chronic Abacterial Prostatitis Using Ultrasound Guided Biopsy

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Summary—A series of 60 patients with a diagnosis of chronic abacterial prostatitis, as defined by the Stamey procedure, was studied by transrectal prostatic ultrasound and subsequent transperineal biopsy of the abnormal areas of the prostate in order to ascertain the role of micro-organisms in this condition.

Histological assessment revealed a chronic inflammatory infiltrate, generally of low grade, in 53 patients (88%). Organisms were isolated from the prostatic tissue of only 9 patients (15%) and were considered to be contaminants from the perineal skin, since treatment with an appropriate antimicrobial agent failed to alter symptoms or affect the leucocyte count in the urine or prostatic fluid. Chronic abacterial prostatitis may be a non-organismal inflammatory process.

The role of micro-organisms in chronic abacterial prostatitis has been a subject of debate for some years (O'Shaugnessy *et al.*, 1956; Meares, 1973; Mårdh and Colleen, 1975; Poletti *et al.*, 1985). The initial searches were concerned with aerobic and anaerobic bacteria in combination with viruses. Mårdh *et al.* (1972) suggested that *Chlamydia trachomatis* organisms (chlamydiae) were important in this condition, though later work by the same group (Mårdh *et al.*, 1978) cast doubt on their original findings. Although Poletti *et al.* (1985) reported that they had isolated chlamydiae from the prostate, this was not our experience in a recent study in which ultrasound guided biopsy was used (Doble *et al.*, 1989). We failed to isolate chlamydiae from the prostate of all 50 patients studied.

An aetiological role has been attributed to ureaplasmas and possibly mycoplasmas by Brunner *et al.* (1983), while Drach *et al.* (1974) regarded gram-positive aerobic organisms to be important in prostatitis.

The aim of this study was to obtain prostatic biopsy material, via a transperineal approach under ultrasound control, from a group of patients with chronic abacterial prostatitis as defined by Drach *et al.* (1978). Tissue obtained so precisely, and having avoided urethral contamination, was subjected to a range of microbial culture techniques in an attempt to ascertain the role of any micro-organisms that might be recovered.

Patients and Methods

Patients attending the sexually transmitted diseases and urology clinics of St Mary's Hospital with a clinical diagnosis of prostatitis were studied. All patients, none of whom had received antibiotics for at least 2 months, underwent a Stamey procedure (Meares and Stamey, 1966) and 60 of them, ranging in age from 19 to 75 years (mean 34), were diagnosed as having prostatitis. The diagnosis was made on finding 10 leucocytes/high-power microscope field (x1000) on examination of the expressed prostatic secretion (EPS), providing there were fewer leucocytes in the urethral (VB1) and bladder (VB2) urine samples, and/or 5 leucocytes/high-power field (HPF) (× 400) in the post-massage urine.

The EPS samples were tested for chlamydiae by a direct immunofluorescence technique (Micro-Trak, Syva). These samples and the urines were

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also tested for aerobic and anaerobic bacteria by routine microbiological methods and, in addition, portions were placed in mycoplasmal medium which was stored at −70°C for subsequent culture for *Mycoplasma* spp. and *Ureaplasma urealyticum* (Taylor-Robinson and Furr, 1981). In addition, all patients had urethral swabs taken to be tested for *Neisseria gonorrhoeae* (Gram-stain and culture) and chlamydiae (MicroTrak, Syva) immediately before the Stamey procedure was conducted. At the same time, venous blood was drawn for chlamydial serology.

After the Stamey procedure each patient underwent transrectal prostatic ultrasound. This was performed using a Bruel and Kjaer 1846 machine with a 5.5 MHz transducer, the patient being in the left lateral position. The findings were recorded on X-ray plate. Previously we noted ultrasonic features of chronic prostatitis (Doble *et al.*, unpublished data), namely high and mid-range density echoes and hypoechoic zones. Under ultrasound guidance, tissue was obtained from these apparently inflamed areas of the prostate via the perineal route. The biopsy tissue was sub-divided, 1 portion being placed immediately in 10% formol saline for routine histological analysis and 1 in 1 ml sucrose-phosphate (2SP) medium without antibiotics, which was stored in liquid nitrogen prior to chlamydial culture. A third portion was pressed on a MicroTrak (Syva) slide to form an impression smear which was examined for chlamydiae by the MicroTrak technique. A fourth portion was placed in mycoplasmal medium and stored at −70°C prior to culture for mycoplasmas and ureaplasmas, a fifth portion was placed in modified Stuart's medium for the culture of anaerobic bacteria, and a final portion was placed in sterile normal saline for routine aerobic bacteriological culture.

Chlamydial growth medium (CMGA: 1 ml) was added to the biopsy material in 2SP medium prior to homogenisation in a ground glass grinder. The homogenate was then made up to a volume of 8 ml with CMGA and 1 ml was added to each of 8 McCoy cell cultures. These were incubated at 37°C, stained with Giemsa reagent and examined by dark ground microscopy for chlamydial inclusions.

The tissue to be cultured for mycoplasmas and ureaplasmas was teased between size 11 surgical blades in 0.4 ml mycoplasmal medium. Then 0.2 ml of the fragmented tissue were transferred to 1.8 ml mycoplasmal medium containing arginine in a screw-capped glass vial (2.5 ml capacity) and the remaining 0.2 ml to 1.8 ml mycoplasmal medium containing urea. Further 10-fold dilutions were made in the respective media up to a dilution of 10^{-4}. The vials were incubated at 37°C and inspected regularly for evidence of any colour change of the media (Taylor-Robinson and Furr, 1981).

The specimen for anaerobic bacteriological culture was spread over appropriate agar medium which was then placed in an Oxoid (Oxoid Ltd) anaerobic jar in 90% nitrogen—10% carbon dioxide. After incubation at 37°C for 5 days, the medium was examined for colonies and any growth subcultured and identified. The remaining tissue was homogenised in a ground glass grinder and inoculated on to blood and McConkey agar. The cultures were incubated aerobically at 37°C and examined at 24 and 48 h.

IgM and IgG antibodies against serovars A–K of *C trachomatis* were sought by an indirect immunofluorescence technique (Thomas *et al.*, 1976)

Results

All 60 patients showed evidence of prostatitis based on the Stamey localisation procedure. The diagnosis in 18 patients was made on the presence of leucocytes in EPS and VB3 samples, and in the remaining 42 patients on leucocytes in the VB3 samples alone.

The areas of abnormal echogenicity on prostatic ultrasound, namely high and mid-range density echoes and hypoechoic zones, were biopsied. In 53 patients, the presence of prostatitis indicated by the Stamey procedure was confirmed by histological examination of prostatic tissue. Insufficient tissue was obtained from 5 patients and the tissue from 2 was normal. Histological features (Table 1) of a

Table 1 Histological Features of Prostatic Biopsies

Feature		*No of patients*
Inflammatory cells		
Acute and chronic		5
Chronic:	grade 1	38
	grade 2	9
	grade 3	5
Granulomatous*		1
Site of inflammation		
Intraglandular		6
Periglandular		34
Stromal		29
Fibrosis		17
Vessel hyaline thickening		14

* *Mycobacterium tuberculosis* excluded.

chronic inflammatory nature in the majority of specimens were generally of low grade. Lymphocytic infiltration was graded on a scale of 1–3, 1 being 5–10 cells/HPF, 2 being 11–15 cells/HPF and 3 being >15 cells/HPF. Lymphocytes were rarely intraglandular and most often were located in the periglandular and stromal regions. Fibrosis was seen in 28% of the biopsies and vessel thickening in 23%.

Gonococci were not isolated from any of the patients. Chlamydiae were detected by direct immunofluorescence technique in urethral specimens from only 2 patients. Furthermore, they were not isolated from the prostatic tissue of any patient, nor were they detected by immunofluorescence in any of the impression smears of prostatic tissue. Sufficient EPS was obtained from 18 patients for examination and in only 1 case were chlamydiae detected by immunofluorescence; a patient in whom chlamydiae were also detected in the urethra.

No patient had evidence of prostatitis as defined by Meares and Stamey (1966), caused by aerobic or anaerobic bacteria. In 4 patients *Mycoplasma hominis* and in 6 patients *Ureaplasma urealyticum* organisms were found in the urine and/or EPS. The numbers of organisms isolated are depicted in Table 2 but only 1 patient had a greater number in the EPS than in VB1 and VB2; he failed to respond to appropriate antimicrobial therapy.

In no case were mycoplasmas and ureaplasmas isolated from the prostatic tissue. Aerobic organisms were cultured from the prostatic biopsies of 7 patients and anaerobic organisms of 3 (Table 3).

Serological examination revealed a chlamydial IgM antibody titre of 1:8 in 1 patient, 1:4 in 7, 1:2 in 3 and 1:<2 in the remaining 49 patients. Examination of chlamydial IgG antibody revealed a titre of 1:32 in 1 patient, 1:8 in 15, 1:4 in 6, 1:2 in 5 and 1:<2 in 33 patients. The patient who had an IgG titre of 1:32 had an IgM titre of 1:4.

Table 2 Isolation of Mycoplasmas and Ureaplasmas from Urine and Expressed Prostatic Secretion

Patient no.	*No. of M. hominis organisms in sample**				*No. of U. urealyticum organisms in sample**			
	VB1	*VB2*	*EPS*	*VB3*	*VB1*	*VB2*	*EPS*	*VB3*
6	—	—	—	10^2	—	—	—	—
26	—	—	—	—	10^3	—	—	—
34	10^2	—	—	—	—	—	—	—
47	—	—	—	—	10^2	10^2	—	—
49	—	—	—	—	10^2	—	—	10^2
50	10^2	—	—	—	10^3	—	—	—
51	—	—	—	—	10^2	10^2	10^3	10^2
52	10^2	—	—	—	10^3	—	—	10^2

* Expressed as colour-changing units/ml.

Table 3 Bacteria Isolated from Prostatic Tissue

Bacteria isolated	*No. of patients*
Escherichia coli	3*
Bacteriodes fragilis	2*
Staphylococcus epidermidis	2
Diphtheroids	1
Bacteroides ureolyticus	1
Pasteurella spp	1

* In one patient both of these *bacteria* were isolated.

Discussion

The debate concerning chronic abacterial prostatitis centres around whether the inflammatory reaction is a response to an infectious agent that has escaped detection by conventional techniques. In this study we used the procedure of ultrasound guided biopsy described initially by Holm and Gamelgaard (1981) and employed by us (Doble *et al.*, 1989) in our previous work on prostatitis. In view of the focal nature of prostatitis (McNeal, 1968), it is not surprising that those who used a blind biopsy technique (Schmidt and Patterson, 1968; Neilsen and Justeson, 1974) did not find the procedure to be of consistent value. However, the areas biopsied in this study appear to have been correctly identified in that tissue from 53 patients (88%) displayed a chronic inflammatory process on routine histology. This is a clear vindication of the ultrasound guided biopsy technique.

In any study of prostatitis it is essential that patients are diagnosed by means of the Stamey localisation procedure (Meares and Stamey, 1966), for a clinical diagnosis alone is quite inaccurate. Even so, the problem of urethral contamination exists, although quantitative estimations of organisms in the third voided bladder (VB3) and EPS specimens can, in part, overcome this problem. In this study, urethral contamination was avoided but the problem of perineal contamination was introduced. We failed to sample the perineal skin for micro-organisms prior to biopsy, in contrast to Nielsen and Justesen (1974), and, therefore, are unable to confirm objectively our suspicion regarding contamination. However, the bacteria that were recovered apparently from the prostatic tissue of a few patients were thought likely to be non-pathogenic, since appropriate antimicrobial treatment for 6 weeks failed to alter significantly the number of leucocytes in the EPS and in the VB3.

The problem of the rich enzyme content of the prostate destroying McCoy cells and so vitiating attempts to culture chlamydiae was overcome by diluting the tissue homogenate and then testing all of the diluted material. Despite this, chlamydiae were not isolated. Furthermore, the absence of chlamydial antigen in the prostatic tissue, as determined by the direct immunofluorescence test, and the low titres of anti-chlamydial antibody suggest that chlamydiae are not implicated directly in chronic abacterial prostatitis. This view is at variance with that of Poletti *et al.* (1985), who claimed to have isolated *C. trachomatis* from 33% of their patients after blind transrectal prostatic aspiration cytology, an inaccurate method compared with ultrasound guided biopsy. In addition, all patients studied by these workers apparently had chlamydiae in the urethra, whereas they were detected in the urethra of only 2 of our patients. One patient in our study had a serum chlamydial IgG antibody titre of 1:32 but a low IgM titre, and an active chlamydial infection was therefore unlikely. Apart from the difference between the results of the 2 studies, it is noteworthy that there is no parallel between them in terms of type of patient or technique used.

Brunner *et al.* (1983) regarded ureaplasmas as pathogenic in a study involving examination of urine and EPS samples only. On only one occasion did we detect these organisms in greater numbers in the EPS than in VB1, and we failed to isolate either them or mycoplasmas from the prostatic tissue. This implies that these micro-organisms do not play an active part in chronic abacterial prostatitis. The same conclusion may be drawn about the role of aerobic and anaerobic bacteria. We have not yet subjected the tissues to virological analysis, but the data suggest that this form of prostatitis is truly abacterial and possibly non-organismal. The accuracy of ultrasound guided biopsy and the transperineal route exclude spurious results caused by contamination of specimens by urethral organisms. However, our findings cannot eliminate the possibility of an infectious agent having been the initiating factor but having since disappeared.

Future research should turn to the investigation of the fundamental nature of the inflammatory process by defining the types and function of the chronic inflammatory cells in the prostate and by comparing these findings to a situation where infection is known to exist, *i.e.* chronic bacterial prostatitis, in order to determine if the 2 conditions are analogous. The role of intraprostatic urinary reflux (Kirby *et al.*, 1982) requires further examination to assess whether this alone produces the inflammatory response seen in chronic prostatitis. In conclusion, we recommend that investigators should distance themselves from the belief that chronic abacterial prostatitis is indeed an active infection and view the problem at the immunological and cellular level.

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Lumbar Pain in Stage 1 Testicular Germ Cell Tumours: a Symptom Preceding Radiological Abnormality

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Summary—In a series of 114 stage 1 testicular tumour patients managed by a surveillance policy there have been 26 relapses. Three of these patients presented with lumbar pain as the first sign of relapse. All 3 were tumour marker non-producers and the onset of pain pre-dated radiological abnormality by up to 4 months. Stage 1 surveillance patients who develop lumbar pain must be considered to be at high risk of relapse to avoid delay in diagnosis which may prejudice survival.

Before the development of effective chemotherapy for testicular germ cell tumours, patients with Stage 1 disease underwent adjuvant retroperitoneal lymph node dissection (RPLND) or radiotherapy in an effort to eradicate microscopic metastases. These approaches resulted in a cure rate of almost 100% in patients with seminomas and over 80% in those with teratomas (Peckham, 1981). However, both treatments are associated with morbidity in a proportion of patients. RPLND may result in retrograde ejaculation (Johnson *et al.*, 1976) and para-aortic radiotherapy will limit bone marrow tolerance to chemotherapy in the 15 to 20% of patients with non-seminomatous tumours who subsequently relapse (Newlands *et al.*, 1986). Since almost all of those who relapse can be salvaged by chemotherapy, many centres have adopted a surveillance policy. With such a policy the relapse rate is around 30% and thus 70% of patients are spared unnecessary treatment (Hoskin *et al.*, 1986; Crawford *et al.*, 1988). However, the effectiveness of relapse therapy depends on early recognition of relapse and this requires careful follow-up by experienced physicians. In the present series, 96% of patients with testicular germ cell tumours who developed metastases had para-aortic nodal involvement and this is usually the initial site of disease (Hitchins *et al.*, 1988). Although the majority of relapses may be detected by rising tumour markers or abnormal radiological investigations, we report 3 patients who developed symptoms referable to the para-aortic region prior to marker or radiological relapse.

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Patients and Methods

Surveillance policy

Since 1980, all patients with testicular tumours referred to this department have been investigated as follows. After a full clinical examination, CT scans of thorax and abdomen and hepatic and para-aortic ultrasound scans are performed. Serum alpha-fetoprotein (AFP) and human chorionic gonadotrophin (HCG) are measured by sensitive radioimmunoassay techniques; full blood count and biochemical profile, including liver enzymes and hydroxybutyrate dehydrogenase (HBD), are requested. Lymphangiography is not routinely performed. Patients with normal tumour markers and no radiological evidence of disease are defined as stage 1. Subsequent follow-up involves regular tumour marker estimations together with chest X-rays and CT scanning as previously described (Crawford *et al.*, 1988).

During this period, 114 patients fulfilled the criteria for stage I surveillance; 37 had pure seminomas and the remainder either non-seminomatous or mixed germ cell tumours; 26 patients (22%) have relapsed and to date all have been salvaged with cisplatin-based chemotherapy.

Patient 1. This 33-year-old man underwent left orchiectomy on 24.11.87. Histology showed a mixed tumour with malignant teratoma and seminomatous elements. He was first seen in this department on 21.12.87, by which time he was complaining of lumbar pain unresponsive to paracetamol + dextropropoxyphene. All investigations were normal and he thus appeared to have stage I disease. However, the lumbar pain became progressively worse and on 13.1.88 a left para-aortic node had increased from 10 mm to 18 mm on ultrasound scan. He was started on cisplatin-based combination chemotherapy and within 24 h his pain had completely resolved. He has now completed chemotherapy and is in complete remission. The tumour markers, including HBD, were never elevated.

Patient 2. This 30-year-old man underwent right orchiectomy on 16.11.87 and histology of the tumour was mixed seminoma + malignant teratoma. He was seen in this department on 4.1.88, complaining of mild low back ache but was generally well and working full time. All investigations were normal and stage I surveillance was instituted. Two months later he noticed that his back pain was becoming increasingly severe but repeat CT scan of the para-aortic region showed no evidence of retroperitoneal lymphadenopathy and the tumour markers and HBD remained within normal limits. Follow-up continued and when seen in July 1988 he had developed pulmonary metastases and a further CT scan showed a 6-cm retroperitoneal mass. Within 3 days of commencing chemotherapy all of his symptoms resolved and he is currently continuing on therapy. His tumour markers were never elevated but the serum HBD became abnormal 4 weeks before overt metastatic disease was detected.

Patient 3. This 44-year-old man underwent right orchiectomy on 12.4.88 and was found to have a pure seminoma. He had noticed some back ache for 2 months prior to surgery but since his operation this had improved. Staging investigations were normal and surveillance was started. Over the next 4 months he lost 4 kg in weight and by August 1988 had developed marked tenderness in the para-aortic region, although the back pain had largely resolved. Repeat ultrasound showed a 25-mm para-aortic node and he was referred for radiotherapy. The tumour markers and HBD were consistently normal.

Discussion

These 3 cases underline the need to maintain a high index of suspicion when dealing with stage I surveillance patients. The majority of non-seminomatous tumours produce either AFP or HCG (Newlands *et al.*, 1986) and in these patients rising marker levels often pre-date the development of symptoms and radiological abnormality (Crawford *et al.*, 1988). However, some 15 to 20% of patients are marker-negative and thus the detection of relapse will rely on symptoms, signs and radiology. Moreover, marker-negative patients may not be readily identifiable unless a pre-surgery marker level is available, since all patients included in the surveillance policy by definition have normal markers. In such patients the serum HBD may provide important additional information. This enzyme has been found to be elevated in a number of different malignancies (Wood *et al.*, 1973) and when present in germ cell trumours appears to parallel disease activity (Bosl *et al.*, 1981). We therefore advocate that HBD estimations should be part of regular monitoring and a rising HBD should be regarded as highly suggestive of recurrent disease.

These patients show that it is not necessary to have abnormally enlarged para-aortic nodes to experience severe pain. At this hospital, nodes less than 2 cm in diameter (by ultrasound and CT criteria) are considered to be normal but our 3 patients all had symptoms, in 1 case requiring opiates to alleviate the pain, from nodes smaller than this. It is possible that in some cases lymphangiography might provide useful additional information, but failure to opacify all nodes at the renal hila is not uncommon.

Our experience suggests that any stage I surveillance patient who develops back pain during follow-up should be considered at high risk of relapse unless there is a clear cut alternative explanation. If tumour markers and CT/ultrasound scans remain normal, careful assessment of serial HBD levels should be made and lymphangiography may be helpful. Particularly close follow-up of such patients is necessary to avoid prejudicing survival by allowing extensive disease to develop.

Acknowledgement

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Tuberculous Epididymo-orchitis: Clinical and Ultrasound Observations

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Summary—The clinical, radiological and ultrasound features of 3 patients presenting with tuberculous epididymo-orchitis are described and the relevant literature reviewed. Scrotal swelling, pain and sinuses are common features at presentation. The presence of a sterile pyuria is a useful sign, but intravenous urography may fail to identify active renal disease. Ultrasound examination revealed testicular involvement in 2 patients. Differentiation from tumour may not be possible, but the presence of epididymal involvement strongly suggests an infective cause. Early surgical biopsy may prove helpful if acid-fast bacilli are not initially identified in early morning urine samples.

Epididymo-orchitis is an unusual manifestation of tuberculosis in the indigenous population of the United Kingdom, although it is more common in immigrants. Genital tuberculosis is usually a disease of sexually active males, with 60% of affected patients aged between 20 and 40 years (Borthwick, 1946). The incidence of genito-urinary tuberculosis has been decreasing over the last 30 years in Europe (Skutil and Gow, 1977) and is now an uncommon clinical presentation. We describe 3 patients with tuberculous epididymo-orchitis and discuss the clinical findings in relation to the radiological and ultrasound appearances. The incidence of genito-urinary tuberculosis reported to the South-East Regional Centre for Tuberculosis Bacteriology over the past 10 years is quoted.

Case Reports

Case 1. A 56-year-old Turkish Cypriot man presented with a 1-month history of right epididymitis associated with urgency, dysuria and frequency of micturition. His symptoms failed to respond to antimicrobial therapy and a painful swelling appeared adjacent to the left testis. His general health was good with no fever, malaise or weight loss; 40 years previously he had undergone a left upper lobectomy for hydatid cyst. Physical examination of the chest and abdomen revealed no abnormality. The right epididymis was irregularly enlarged with a lax hydrocele. The left testis and epididymis were normal but there was a firm, tender, 1-cm swelling adjacent to them. The clinical appearance was suggestive of tuberculous epididymitis. Although there was a sterile pyuria the urinary tract appeared to be normal on intravenous urography. On ultrasound there was a small right-sided hydrocele, an enlarged right lower pole epididymis and a normal testis. There was a 1·4-cm cyst in the upper pole of the left epididymis but the testis was normal Lying separate and inferior to both the left epididymis and testis was a 1.6-cm solid mass. An excision biopsy of the painful swelling in the left scrotum confirmed the diagnosis of tuberculosis and early morning urine cultures grew *Mycobacterium tuberculosis* 6 weeks later. A repeat scan after 6 months' treatment was normal apart from the cyst in the upper pole of the left epididymis.

Case 2. A 31-year-old Nigerian man presented with a 6-month history of a tender right testicular swelling. He had no urinary symptoms, his general health was good and there was no significant past medical or family history. Physical examination of the chest and abdomen was unremarkable. The right epididymis was enlarged, irregular and hard and the lower pole was associated with a small scrotal sinus and a lax hydrocele. The left testis and epididymis were normal.

Examination of a mid-stream specimen of urine revealed a sterile pyuria. A chest X-ray was normal. An intravenous urogram revealed dilatation of the right middle pole calyx with narrowing at the neck suggestive

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of a stricture and distortion of the upper pole caliceal neck, right renal pelvis and ureter (Fig. 1). The left kidney, ureter and the bladder appeared normal. Ultrasound scan of the right testis revealed a pattern of decreased reflectivity throughout (Fig. 2) in comparison with the normal left testis. In the upper pole of the right testis there was a 2.8-cm well circumscribed area of low reflectivity associated with posterior acoustic enlargement (Fig. 3). The epididymis was enlarged and of low reflectivity A provisional diagnosis of tuberculous infection with abscess formation was made. Acid-fast bacilli identified subsequently as *M. tuberculosis* were cultured from early morning urine specimens, confirming the clinical diagnosis of renal and epididymal tuberculosis, and treatment was started.

A repeat scan after 6 months' treatment showed the abscess in the upper pole of the right testis to be 1.8 cm in diameter. The appearance of the remainder of the testis and the epididymis was unchanged.

Case 3. A 47-year-old Caucasian male presented with a 1-year history of recurrent urinary tract infections. Over several months his left testis had become swollen and had discharged pus on one occasion. He was otherwise well. He had previously been investigated for a deformed left femoral head which was thought to have been secondary to Perthes' disease rather than tuberculosis The left testis was hard and enlarged; physical examination was otherwise normal. A mid-stream urine specimen revealed a sterile pyuria. A chest X-ray was normal. Ultrasonography revealed a rounded echo-poor lesion in the lower pole of the left testis (Fig. 4). The remainder of the testis, which was enlarged, had a heterogeneous pattern of reflectivity such that a tumour could not be excluded The right testis and epididymis were normal.

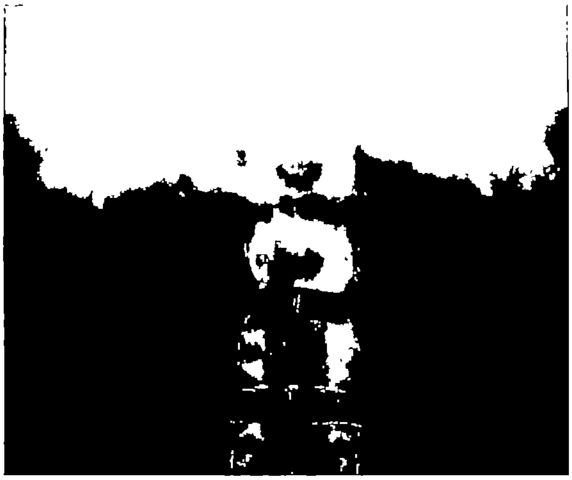

Fig. 1 Post-micturition film of IVU showing a dilated right middle pole calyx with a possible stricture at the neck and distortion of the upper pole calyceal neck, right renal pelvis and ureter

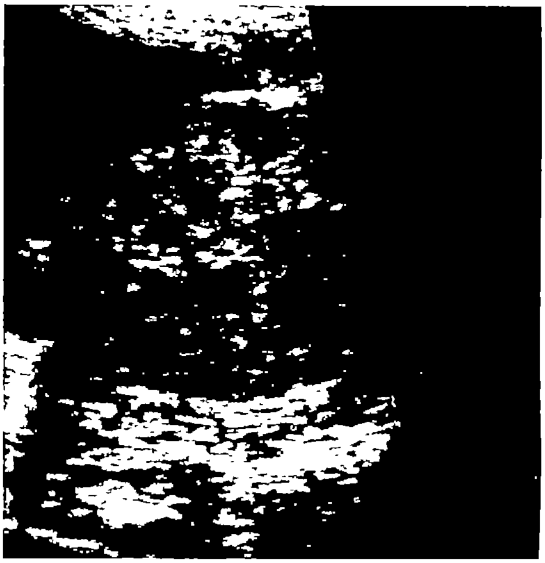

Fig. 2 Ultrasound scan showing a heterogeneous pattern of decreased reflectivity throughout the right testis.

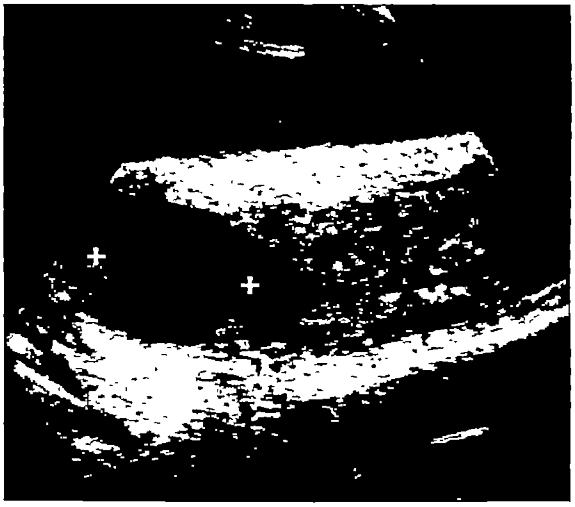

Fig. 3 Ultrasound scan revealing a 2·8-cm area of low reflectivity with posterior acoustic enhancement in the upper pole of the right testis consistent with an abscess.

A plain abdominal X-ray and intravenous urogram revealed calcification in the right kidney and prostate (Fig. 5), with clubbing and dilatation of the major calyces of the right kidney (Fig. 6). The left kidney and ureter were normal. The left hemi-scrotum was explored, the irregularly enlarged and calcified epididymis was excised and a biopsy of the testis was taken. Cystoscopy revealed a small capacity bladder with an inflamed trigone.

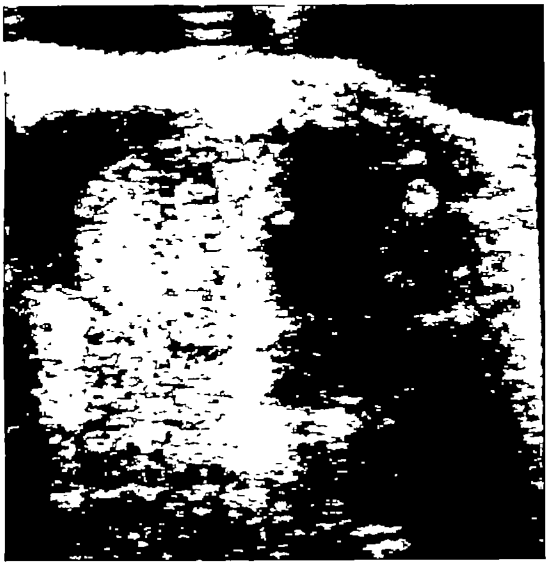

Fig. 4 Ultrasound scan revealing an area of low reflectivity in the lower pole of the left testis

Histological examination of the testicular tissue and thickened capsule showed areas of caseation, necrosis and epithelioid granulomatous formation in between seminiferous tubules. Ziehl-Nielson staining revealed acid-fast bacilli and early morning urine culture confirmed the diagnosis of infection with *M. tuberculosis*.

Discussion

There has been a decline in the incidence of genital tuberculosis over the past 30 years in the United Kingdom and most cases are associated with urinary tract tuberculosis (Gow, 1971). The number of patients with tuberculosis reported to the South-East Regional Centre for Tuberculosis Bacteriology at the Dulwich Public Health Laboratory in 1988 was 1,161; renal and genital tuberculosis accounted for 42 and 8 cases respectively. The number of reported cases of pulmonary, renal, genital and cervical tuberculosis over the previous 10 years is shown in the Table. These figures confirm the gradual decline in the numbers reported to the Regional Centre.

Tuberculous epididymitis occurs most commonly between the ages of 20 and 50 years, during the time of greatest sexual activity, and at least 70% of patients have a history of previous tuberculosis. Common presenting problems are scrotal swelling, pain, discharge and sinuses (Ross *et al.*, 1961). The presence of abscess or sinus formation indicates advanced widespread scrotal disease. All 3 patients

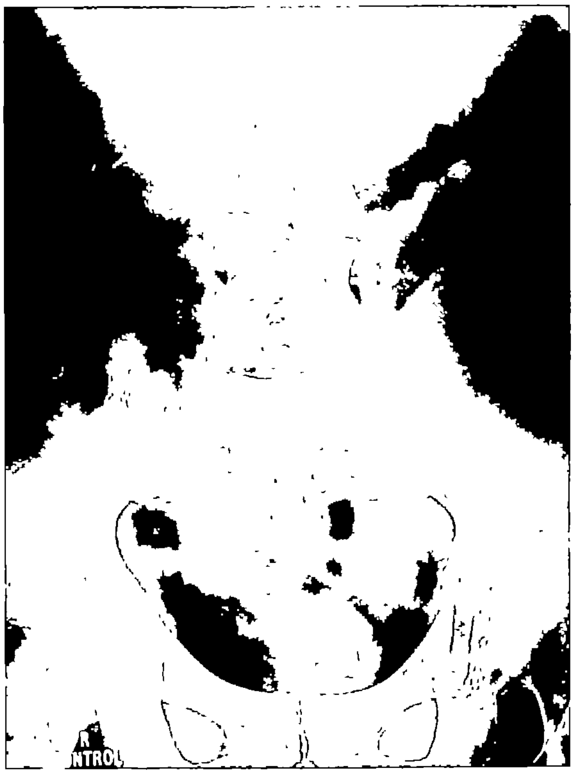

Fig. 5 Right renal and prostatic calcification visible on a plain abdominal X-ray Note the abnormal appearance of the left femoral head

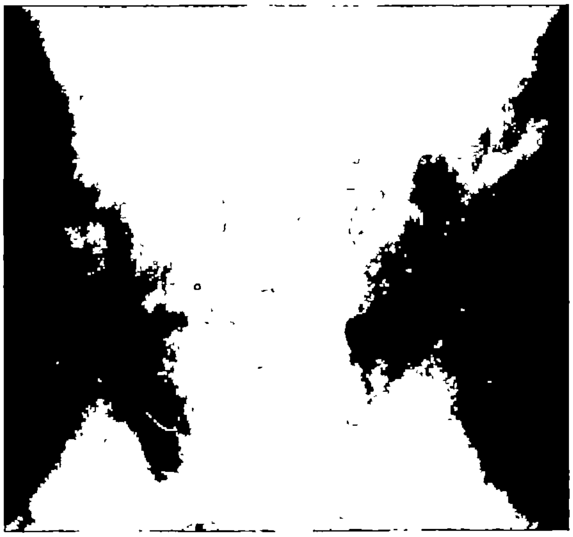

Fig. 6 Clubbing and dilatation of the major calyces of the right kidney

Table Cases of *Mycobacterium tuberculosis* Reported to the South-East Regional Tuberculosis Centre

	Pulmonary	*Renal*	*Genital*	*Cervical*	*Total*
1978	1218	87	25	224	1777
1980	1259	87	16	206	1788
1982	1060	80	15	157	1483
1984	951	36	8	122	1298
1986	803	42	8	139	1307
1988	792	42	8	149	1161

described had a sterile pyuria, which remains a valuable pointer to the diagnosis of genito-urinary tuberculosis. A sterile pyuria was absent in only 12% of urine specimens from which *M. tuberculosis* was grown in a series reported by Gow (1971). Intravenous urography may be normal in up to 25% of patients with tuberculosis epididymo-orchitis (Ferrie and Rundle, 1983) and has been considered an insensitive way of documenting renal tuberculosis disease (Gorse and Belshe, 1985).

Tuberculous orchitis is considered to be rare, as it was found in only 1 of 32 patients with genito-urinary tuberculosis described by Rosenberg (1963). Christiansen (1974), however, noted testicular involvement in 23% and Gow (1966) identified it in 14% of 83 patients with tuberculous epididymitis. Orchitis is thought to occur by contiguous spread from the epididymis and therefore reflects a later stage of the disease, although some authors consider it to be blood-borne. The incidence of orchitis in miliary tuberculosis, however, appears to be less than 5% (Loughnane, 1944; Medlar, 1949). Epididymal involvement is likely to be secondary to blood-borne infection (Gow, 1971), but it may occur via the urinary tract (Veenema and Lattimer, 1957) or possibly from the pelvic lymphatics (Duchek and Winblad, 1973).

The patients were treated with a 3-month course of ethambutol (15 mg/kg body weight) and 9 months of isoniazid (200–300 mg) and rifampicin (8–12 mg/kg body weight) given as single daily doses. Pyridoxine hydrochloride (10 mg daily) was given to prevent isoniazid neuropathy if the dose given exceeded 5 mg/kg. Sensitivities were available 3 weeks after the start of treatment. Shorter courses of chemotherapy have been advocated (Gow and Barbosa, 1984).

The ultrasound appearances of tuberculous epididymitis are non-specific. Both infection and tumour of the testis may appear as focal or diffuse areas of low reflectivity. Intratesticular lesions of low or absent reflectivity are most commonly tumours, but metastatic lesions and some primary tumours may occasionally present with areas of increased reflectivity due to associated haemorrhage, fibrosis or calcification. According to Blei *et al.* (1983), markedly increased reflectivity is found in inflammatory and vascular lesions of the testis, but not with tumours. Vick, *et al.* (1983) also thought that a scrotal mass of high reflectivity was likely to be benign. The presence of epididymal involvement strongly suggests a non-neoplastic process.

Ultrasound scans of 2 of the patients presented here (Cases 2 and 3) revealed a heterogeneous pattern of low reflectivity. Case 2 had an abscess in the upper pole of the testis and an associated enlargement of the epididymis, making infection the most likely cause. Ultrasound scan of the testis was normal in Case 1.

The investigation of scrotal swellings with high resolution ultrasound using a 7.5 mg MHz or 10.0 MHz probe is a rapid and helpful non-invasive method of assessing scrotal contents, particularly in the presence of a hydrocele (Krone and Carroll, 1985). Ultrasound will readily detect the presence of testicular abnormality, but differentiation of infection from tumour is often not possible on ultrasound appearances alone. Ultrasound is particularly helpful in distinguishing intra- from extra-testicular lesions. Biopsy may be needed to establish the definitive diagnosis and proved useful in providing an early diagnosis in 2 of our cases. We would recommend early surgical exploration in cases of suspected tuberculous epididymitis as advocated by Gow (1981) and Gorse and Belshe (1985) if the initial examination of early morning urine samples does not identify acid-fast bacilli.

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Treatment and Complications of Fournier's Gangrene

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Summary—Ten patients with Fournier's gangrene were seen over an 11-month period; 3 had indwelling urethral catheters, 3 had preceding perineal infection and 6 had a history of alcohol abuse.

An average of 2.1 operations was required per patient and the average hospital stay was 41 days. The mortality rate was 20%; 7 patients developed acute renal failure and 5 developed adult respiratory distress syndrome. Early treatment of these complications should help to reduce the mortality of this disease.

Since the original description by Fournier (1883), over 400 cases of Fournier's gangrene have been reported (Berg *et al.*, 1986). Fournier's description consisted of abrupt onset of scrotal pain and swelling in young, previously healthy males, with rapid progression to gangrene and absence of a specific aetiological agent.

Pathologically, the process is a subcutaneous infection with oedema and acute inflammation leading to necrosis (Campbell, 1955). There may be subcutaneous vessel thrombosis with obliterative endarteritis and gangrene of the overlying dermal and epidermal tissues.

Culture of the pus or tissue usually reveals a polymicrobial infection, including gram positive and negative aerobes as well as anaerobes (Lamb and Juler, 1983). *In vivo* synergism has been demonstrated previously in mixtures of anaerobic and aerobic bacteria (Onderdonk *et al.*, 1976) and the rapidly destructive nature of this disease probably relates to this synergistic effect.

Fournier's gangrene may occur at any age, but it has been suggested that the age of peak incidence has been increasing. In addition, there appears to be a trend towards a less acute onset (Jones *et al.*, 1979).

We have treated 10 patients with this condition, and present our findings and treatment protocol.

Patients and Methods

In an 11-month period, 10 male patients presented with genital gangrene. Details of past medical and social history were obtained. Prodromal symptoms and specific aetiological factors were recorded, as were bacteriological and histopathological findings. The patients' response to treatment and the development of complications were also studied.

Results

The patients ranged in age from 30 to 79 years (average 60.5). Six patients were Caucasian and 4 were black. The prodromal period ranged from 1 to 20 days and symptoms included malaise, diarrhoea, vague penoscrotal discomfort and varying degrees of voiding dysfunction. At presentation, the symptoms and signs included penoscrotal pain, erythema and oedema, fever and gangrene, and leucocytosis. Three patients showed systemic effects of toxicity, namely haemodynamic instability, altered mentation and fever.

Nine patients had an identifiable predisposing cause (Table 1). This was associated with an indwelling catheter in 3 cases and preceding perineal infection in another 3; 6 patients gave a history of alcohol abuse with complications including delirium tremens. Only 2 patients had a history of diabetes mellitus.

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Table 1 Aetiology, Associated Conditions, Age and Prodromal Period

Patient no.	*Aetiology*	*Associated condition*	*Age (years)*	*Prodromal period (days)*
1	Perirectal abscess	Diabetes	56	8
2	Penile pain at coitus	Alcohol abuse	38	2
3	Perirectal abscess	Steroid-dependent COPD	78	?
4	—	Alcohol abuse	40	5
5	Scrotal furuncle	—	30	20
6	Traumatic catheter insertion, epididymo-orchitis	Alcohol abuse	70	7
7	Erosion of catheter	Alcohol abuse	69	1
8	Urethral stricture	Alcohol abuse	79	2
9	Blocked catheter	Alcohol abuse, diabetes	69	3
10	Diverticulitis	—	76	3

In all cases, tissue, blood and urine cultures were obtained. In 9 patients, 3 or more different bacteriological species were isolated (Table 2). In 3 patients, however, only aerobic microbes were obtained. Of the aerobic organisms, *Escherichia coli* and streptococci were most frequently found.

Treatment consisted of a broad spectrum triple antibiotic regime using an aminoglycoside with either clindamycin or metronidazole, and either penicillin or ampicillin. Urgent surgical treatment was required in all cases, consisting of debridement of all obviously necrotic or doubtfully viable tissue. Retrograde urethrography or sigmoidoscopy was carried out initially if urethral or rectal pathology was suspected. An abnormal retrograde urethrogram indicates the need for suprapubic urinary drainage and, similarly, abnormal sigmoidoscopy may indicate the need for proximal colostomy. Eight patients required suprapubic urinary diversion because of the urethral aetiology in 4 cases and the extensive periurethral disease in the remainder. One patient with diverticulitis also had a defunctioning colostomy performed. Post-operatively, wet-to-dry dressing changes, with 0.5% Dakin's solution, were used. After 48 h, twice daily hydrotherapy was instituted.

Five patients required repeat surgery for further debridement between 1 and 7 days after the initial operation (Table 3). Six patients had testes placed in medial subcutaneous thigh pouches and 1 patient required bilateral orchiectomy because of associated epididymo-orchitis and abscess formation. Split thickness skin grafting to cover large epithelial defects was carried out in 4 patients. This was performed between 19 and 27 days after the initial debridement.

An average of 2.1 operations was required per patient and the average hospital stay was 40.8 days (range 24–63).

Histological examination in all cases confirmed oedema, acute inflammation and necrosis of the subcutaneous tissue.

In view of the extensive tissue loss and gross sepsis, all patients received parenteral nutrition

Table 2 Organisms Isolated from Tissue and Pus

Patient	*Aerobes*		*Anaerobic*	
no.	*G+*	*G−*	*G+*	*G−*
1	Haemolytic streptococcus		*Actinomyces, Israelii*	*Bacteroides melaninogenicus*
2	Haemolytic streptococcus	Actinobacter, Pseudomonas		
3		Proteus, *E. coli*	Peptostrep.	*Bacteroides fragilis*
4	Haemolytic streptococcus	*E. coli*, mixed	Corynebacteria	
5		Pseudomonas, *E. coli*		
6	Enterococcus		Peptostrep	Fusobacterium
7	Enterococcus	*E. coli*, Enterobacter, *Proteus*		
8	*Staph aureus*			*Bacteroides fragilis*
9	*Staph. aureus*	Enterobacter, Citrobacter		Fusobacterium
10	*Staph aureus*	*Morganella morgani, E coli*	Peptostrep., *Clostridium perfringens*	

Table 3 Operative Treatment, Hospital Stay and Complications

Patient no	*Surgery*	*No. of procedures*	*Days in hospital*	*Post-operative complications*
1	Debridement, debridement 1 week later and medial testis thigh pouch	2	24	—
2	Debridement, debridement 48 h later, medial testis thigh pouch and suprapubic catheter placement	2	63	ARDS, acute renal failure, pneumonia and GI bleed, died
3	Debridement, medial testis thigh pouch, suprapubic catheter placement	1	30	ARDS; died
4	Debridement, medial testis thigh pouch, debridement 48 h later, suprapubic catheter placement; skin graft day 19	3	30	—
5	Debridement	1	45	ARDS, renal failure, intercerebral haemorrhage
6	Debridement, suprapubic catheter placement, orchiectomy; skin graft day 24	2	58	Acute renal failure
7	Debridement, suprapubic catheter placement, skin graft day 27	2	58	Acute renal failure
8	Debridement, suprapubic catheter placement	1	35	ARDS, acute renal failure
9	Debridement, suprapubic catheter placement; debridement 24 h later, medial testis thigh pouch; debridement 48 h later; skin graft 3 weeks, revised	4	28	Acute renal failure, ARDS, pneumonia
10	Debridement, surpapubic catheter placement, diverting colostomy, debridement 48 h later, medial testis thigh pouch; debridement day 4	3	51	Acute renal failure, pneumonia

starting within the first 48 h after surgery and continuing until the patient was able to maintain an adequate oral intake.

The patients showed no common factors in socio-economic status, occupation, dwelling or recreation.

Two patients died. Both had developed adult respiratory distress syndrome (ARDS). One also developed acute renal failure with pneumonia and a gastrointestinal bleed. Of the remaining 8 patients, 6 developed acute renal failure. This was complicated by ARDS in 3 patients, pneumonia in 2 and an intracerebral haemorrhage in 1 (Table 3). As an illustration, we present case 7.

Case Report

A 69-year-old man was referred to the dermatological department, complaining of an irritating, red area of skin suprapubically. He had an indwelling Foley catheter because of urinary incontinence following a TURP and stroke 2 years earlier. This had been changed 3 days prior to presentation. He was initially treated with a steroid cream but 2 days later he developed genital discomfort with tenderness, oedema and a patch of discoloured skin on the penis (Fig. 1). A diagnosis of Fournier's gangrene was made and he was started on clindamycin, cefazolin and penicillin. A cystourethrogram was performed and this showed marked extravasation from the bulbo-penile urethra (Fig. 2). Surgical exploration revealed gross subcutaneous necrosis extending along the abdominal wall, penis and scrotum. Part of the urethra was completely destroyed. A suprapubic catheter replaced

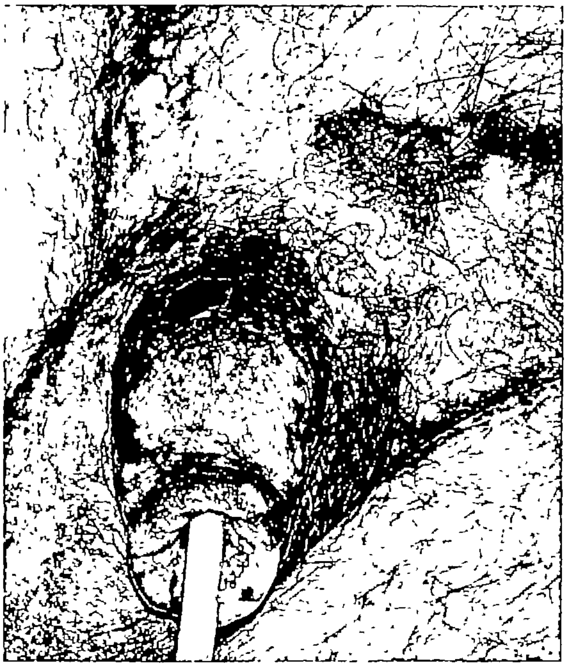

Fig. 1 Appearance of lesion at presentation.

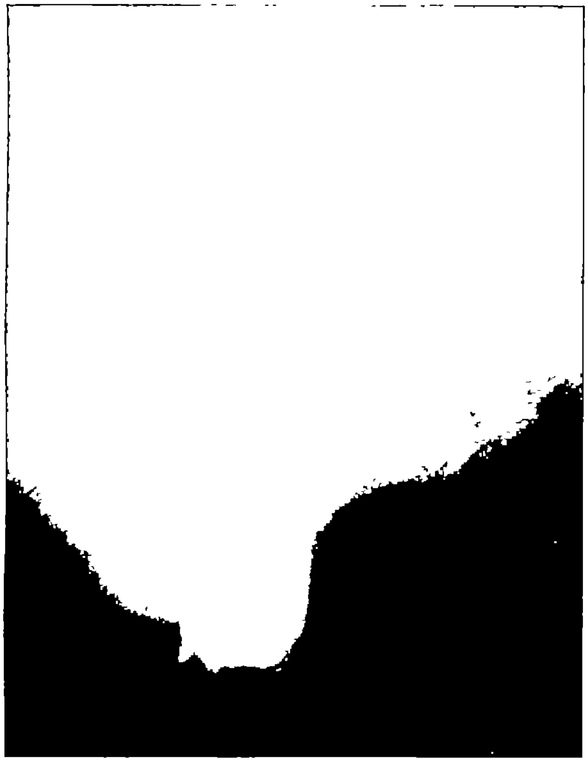

Fig. 2 Pre-operative cystogram showing extravasation

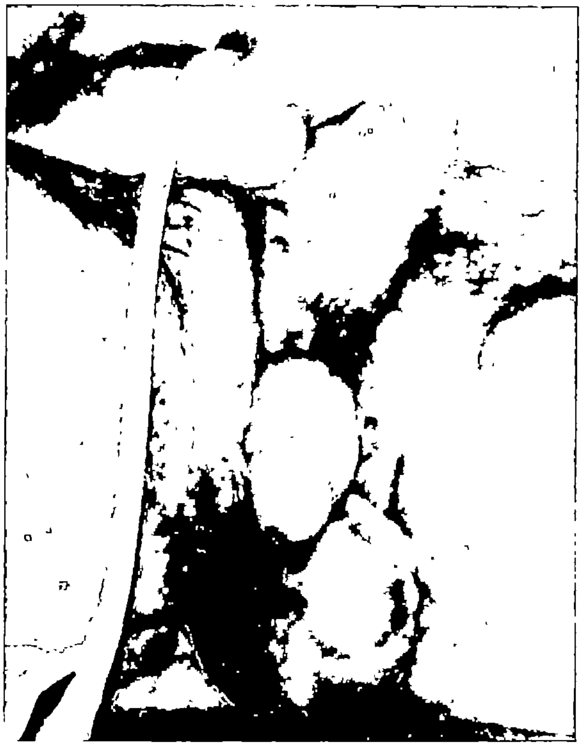

Fig. 3 Final appearance on discharge

the urethral one Post-operatively, the patient developed acute renal failure, which resolved, and the exposed surface was suitable for split thickness skin grafting on the 27th post-operative day. This healed slowly and the patient was discharged on the 58th post-operative day with full skin cover and a suprapubic catheter (Fig. 3).

Discussion

The syndrome of acute fulminant genital gangrene remains an uncommon but serious problem. The incidence was calculated at 1/7500 patients by Bejanga (1979). The comparatively older age at onset and prolonged prodromal period in most of our patients is consistent with the changing presentation noted previously (Jones *et al.*, 1979). The occurrence of this disease as a complication of urethral catheterisation and perineal sepsis has been noted (Flanigan *et al.*, 1978, Spirnak *et al.*, 1984). Only 2 of our patients had a history of diabetes compared with 6 who gave a history of alcohol abuse. Spirnak *et al.* (1984) reported only a 25% incidence of alcohol abuse, but a relatively high incidence of diabetes has been noted (Gerber and Peterson, 1973). Both of these diseases can cause impairment of immunity, while diabetes also causes distal arterial disease (Mendelson, 1970; Quie and Cates, 1977).

Treatment with multiple antibiotics is necessary in Fournier's gangrene because of the polymicrobial nature of the infection. This therapy can be based on penicillin for streptococci, either clindamycin or metronidazole for anaerobes, and an aminoglycoside for activity against the gram negative aerobes. In view of the high incidence of renal failure found in this series, it is necessary to monitor carefully the dosage of antibiotics, particularly the nephrotoxic aminoglycosides.

To ensure a successful outcome it is essential that early debridement of the gangrenous area be performed. We debrided all frankly necrotic tissue and any further tissue where viability seemed doubtful, but 5 patients still required further debridement. It is important that, in these patients, careful observation of the exposed surface is followed up by early repeated debridement where indicated. As has been noted in previous reports (Jones *et al.*, 1979), the testes and spermatic cords are generally not affected by the disease, although 1 of our patients who appeared to have a pre-existing epididymo-orchitis did develop testicular abscesses and required orchiectomy. Any extensive tissue defect can be covered by a split thickness skin graft once infection has resolved and a base of healthy granulation tissue is present. This situation was achieved between 19 and 27 days after initial debridement in the 4 patients who required grafting. The use of gracilis musculocutaneous flaps to cover deep tissue defects has also been described (Banks *et al.*, 1986).

Mortality rates of 13 to 60% have been reported (Flanigan *et al.*, 1978; Jones *et al.*, 1979), compared with 20% in this series. The serious systemic complications of ARDS and acute renal failure occurred in 5 and 7 of our patients respectively. The high incidence of these complications indicates the importance of close monitoring for early signs of their development, since both are more successfully treated if detected early.

Because of extensive tissue loss and gross sepsis, these patients will have increased metabolic needs which are best treated by parenteral nutrition. It is our policy to institute this within the first 48 h.

It has also been shown that hyperbaric oxygen is beneficial and may help to reduce mortality and the spread of gangrene, especially if used early in the disease (Ellis and Mandal, 1983; Eltoroi *et al.*, 1986).

Fournier's gangrene still carries a significant mortality rate. Early aggressive antibiotic therapy with debridement of all necrotic tissue is vital and further debridement must be carried out when indicated. Colostomy may be required in patients with a colorectal aetiology, and suprapubic urinary diversion in those with urethral or extensive periurethral disease. Patients must be carefully monitored for early signs of ARDS and renal failure, as these are the major systemic complications leading to death. Awareness of their frequency should assist in their early detection and treatment and thus lead to a decrease in the high mortality rate of this disease.

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Case Reports

Testicular Metastases from Prostatic Carcinoma

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Case Report

A 77-year-old retired electrician presented with a progressively enlarging painless left testis of 3 months' duration. He had a past history of transurethral prostatectomy in 1984. The pathology showed micro-acinar prostatic carcinoma. At that time, a positive bone scan together with a raised serum prostatic acid phosphatase (24 u/l) revealed asymptomatic bone metastases. He was treated with stilboestrol and his acid phosphatase returned to normal. He returned in 1987 with difficulty in voiding, frequency and nocturia following poor compliance with his stilboestrol. Cystoscopy and raised acid phosphatase (7 u/l) confirmed recurrence of the prostatic carcinoma. A urethral dilatation resolved his symptoms and he recommenced stilboestrol.

On examination his left testis was enlarged, hard and irregular. The right testis was atrophic, in keeping with years of stilboestrol treatment. A clinical diagnosis of malignant testicular tumour was made. A left orchiectomy through an inguinal approach together with a right subcapsular orchiectomy was performed. Pathology showed a 55 × 40 × 35 mm testis containing multiple nodules of metastatic adenocarcinoma. Immunohistochemistry confirmed the derivation from prostate.

Comment

It is interesting that the testis should be such a rare site for metastasis. The relatively low scrotal temperature may partly explain this. The testicular "distal" anatomical site may also play a role.

Lung and prostate are the commonest tumours metastasising to testis, followed by GI tract, melanoma, kidney, pancreas and adrenal tumours (Werth *et al.*, 1982; Grignon *et al.*, 1986). Advanced years is a feature of these patients.

The spread of prostatic carcinoma is probably along the vas deferens via the lymphatic channel or through the lumen or substance of the vas (Hanash *et al.*, 1969).

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An Unusual Presentation of a Urachal Remnant

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Since they were first reported in 1550 by Bartholomaeus Cabrolius (Begg, 1927), a variety of urachal remnants have been described (Blichert-Toft and Nielsen, 1971). The common feature is their connection to the umbilicus. We describe a case which demonstrates that such an anatomical arrangement does not always exist.

Case Report

J. R., an 18-month-old Caucasian female, presented with a suprapubic midline sinus opening 4 cm below the umbilicus. This had been present since birth and had been noted to discharge clear yellow fluid. A urine specimen, ultrasound scan, cystoscopy and micturating cystogram were all normal. The sinus was explored and found to extend caudally to the symphysis pubis and thence cranially to the dome of the bladder and was excised with a cuff of bladder. No cranial extension of the sinus could be traced in the direction of the umbilicus. Post-operatively, she made an uneventful recovery. The histology showed a fistula track lined with transitional epithelium.

Comment

The urachus is a vestigial fibromuscular tube extending from the apex of the bladder to the umbilicus which, after birth, involutes to become a fibrous cord, the median umbilical ligament (Begg, 1930).

Congenital patent urachal anomalies present early in life and all reports and standard texts agree that these drain at the umbilicus. This case clearly did not drain at the umbilicus and yet was a patent urachal remnant.

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Acute Retention due to Multiple Urethral Calculi—an Unusual Presentation of Bladder Tumour

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Case Report

A 48-year-old man presented with acute urinary retention. Two months previously he had passed a calculus but otherwise had no urological symptoms. Examination revealed a tender bladder, a degree of meatal stenosis and multiple stones within the penile urethra. A radiograph (Fig.) confirmed calculi in the distal urethra and a further small stone in the prostatic urethra; abdominal films showed no evidence of upper tract calculi. A suprapubic catheter was inserted.

At operation, a meatoplasty was performed and the urethral calculi were removed. Cystoscopy revealed numerous small spiculated stones attached to injected bladder mucosa. The calculi were evacuated and multiple bladder biopsies were taken Histological examination confirmed an invasive, poorly differentiated (grade III) transitional cell carcinoma.

Comment

The association of transitional cell carcinoma and calcification is well recognised. Acute retention due to multiple urethral calculi has been reported in a patient with medullary sponge kidneys (Shah, 1983), but this appears to be the first bladder tumour to present in this way.

This case demonstrates the value of cystoscopy in patients with multiple urethral calculi and the importance of bladder biospy where the cystoscopic abnormalities are more extensive than may be anticipated with bladder stones or following catheterisation.

Fig.

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A Rare Cause of Intermittent Painful Penile Swelling

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Case Report

A 75-year-old man was admitted with a myocardial infarct. He complained of impotence and involuntary painful swelling of his penis which occurred when he was standing or walking.

Past medical history included an abdominal perineal resection of rectum for adenocarcinoma 4 years previously, Paget's disease of his pelvis and a TURP for benign nodular hyperplasia 18 months previously. Examination revealed engorgement of the penis commencing 5 min after standing, becoming maximal after 10 min, which caused pain along the shaft of the penis and perineum. The penis hung in the dependent position and did not become erect; both corpora became engorged but remained easily compressible. There was no oedema of the penile or scrotal skin or ankles. Examination of the abdomen and perineum was normal. On lying, the swelling resolved over 20 min, although the pain persisted for 2 h.

A penile cavernogram was unhelpful. However, a pelvic CT scan (Fig. 1) and a bilateral iliac arteriogram demonstrated recurrent rectal tumour in the pelvis obstructing both common iliac veins (Fig. 2).

Comment

Swelling of the penile and scrotal skin is occasionally seen in patients with recurrent pelvic tumour following abdominal perineal excision of rectum. It is usually confined to the subcutaneous tissues and oedema of the lower limbs is usual, the corpora remaining unaffected (Gilbertson, 1960; Goligher, 1985). In our experience this case is unique in that the venous drainage of the corpora was affected selectively.

We conclude that engorgement of the penis resulted from impaired venous drainage of the corpora. We cannot explain why swelling only occurred on standing, but it was probably due to altered venous drainage in this position.

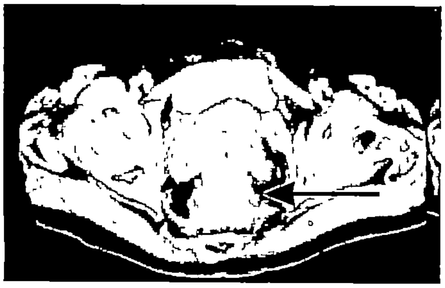

Fig. 1

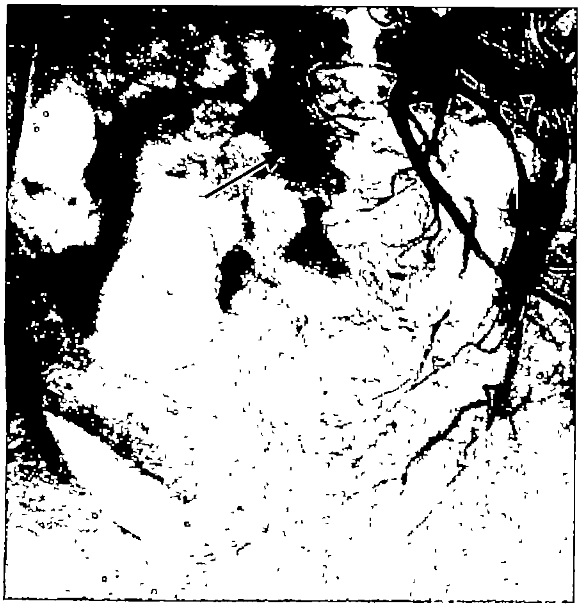

Fig. 2

Acknowledgement

We thank Dr E. M. McIlrath, Consultant Radiologist, for performing the investigations in this case

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Prostatic Adenocarcinoma with Endometrioid Features Treated with Oestrogen

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Case Report

A 62-year-old man complained of dysuria and urethral bleeding. At cystoscopy, papillary tumours were found in the posterior urethra around the verumontanum. Transrectal digital examination showed a large elastic tumour at the cephalad of the right lobe of the prostate. Computed tomography (CT) showed a large cystic tumour of the right seminal vesicle (Fig. 1) and enlargement of the right obturator lymph node. Bone scintigraphy showed no abnormal findings. Serum prostatic specific acid phosphatase (PSAP) and prostatic specific antigen (PSA) were 6.7 ng/ml (normal range < 3.0) and 61 ng/ml (< 3.6) respectively. Both transurethral resection of the papillary tumour of the urethra and transurethral biopsy of the prostate around the verumontanum showed papillary adenocarcinoma of the prostate with endometrioid

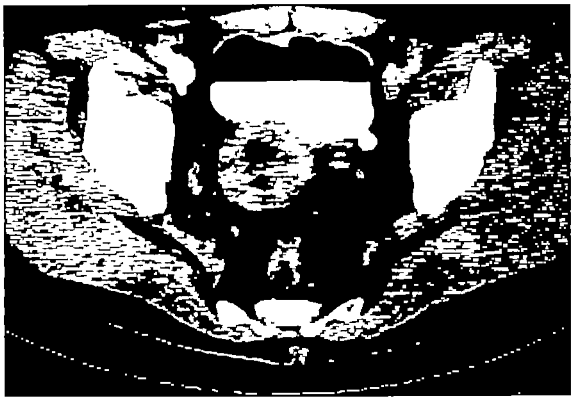

Fig. 1 Pelvic CT showing tumour of right seminal vesicle

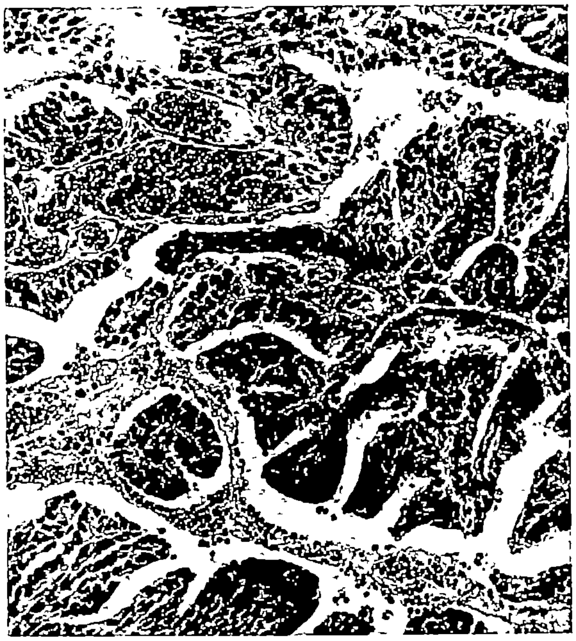

Fig. 2 (H and E ×277)

features (Fig. 2). The tumour exhibited prominent papillary fronds with fibrovascular stalks. Both PSAP and PSA staining, using the peroxidase-antiperoxidase method, were positive. Oestrogen therapy with diethylstilboestrol-diphosphate was started; after 10 months' treatment, CT and rectal examination showed that the seminal vesicle tumour had greatly decreased in size. PSAP and PSA had decreased to 0.1 and 1.5 ng/ml respectively.

Comment

The origin of the papillary adenocarcinoma arising around the verumontanum has been discussed (Gillatt *et al.*, 1986) since Melicow and Pachter (1967) first advocated the term "endometrial carcinoma of the prostatic utricle". Immunohistochemical and ultrastructural studies have demonstrated that this type of carcinoma is identical to the adenocarcinoma of the prostatic duct (Bostwick *et al.*, 1985), and anti-androgen therapy is proposed.

Most papillary adenocarcinomas of the prostate are coexistent with ordinary acinar carcinoma, and only a few patients with a pure papillary adenocarcinoma which responded to anti-androgen therapy have been reported (Epstein and Woodruff, 1986). The present case showed a good clinical effect from the use of oestrogen for a pure papillary adenocarcinoma arising from the prostatic urethra and invading the seminal vesicle. We think that prostatic adenocarcinoma with endometrioid features should be treated in the same way as ordinary prostatic carcinoma.

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Bromocriptine-associated Retroperitoneal Fibrosis Presenting with Testicular Retraction

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High dose bromocriptine therapy for Parkinsonism has been implicated in the aetiology of retroperitoneal fibrosis (RPF) (Bowler *et al.*, 1986; Demonet *et al.*, 1986).

We report a similar case presenting with testicular retraction.

Case Report

A 72-year-old man presented with a 2-month history of left testicular retraction and swelling of the right thigh. He had a 2-year history of Parkinsonism successfully treated with bromocriptine 70 mg daily.

Examination showed lymphoedema of the right thigh. The left testis was palpable in the inguinal canal. The patient was normotensive and urine microscopy negative. Investigations revealed an ESR of 41 mm/h, urea 9.5 mmol, creatinine 137 mmol, creatinine clearance 41 ml/min. Chest X-ray was normal. Intravenous urography demonstrated a moderately dilated ureter on the right with medial deviation at L4 and no function on the left (Fig.). CT scan showed soft tissue reaction obstructing the left ureter. A diagnosis of RPF, presumably secondary to bromocriptine therapy, was made.

Treatment consisted of the insertion of bilateral double-J stents, a 6-month reducing course of steroids and substitution of bromocriptine with L-dopa

Follow-up urography at 6 months showed good bilateral function. Urea and creatinine were normal (creatinine clearance 64 ml/min), the testis had descended into the scrotum and the lymphoedema had resolved. The Parkinsonism has been less well controlled with L-dopa therapy.

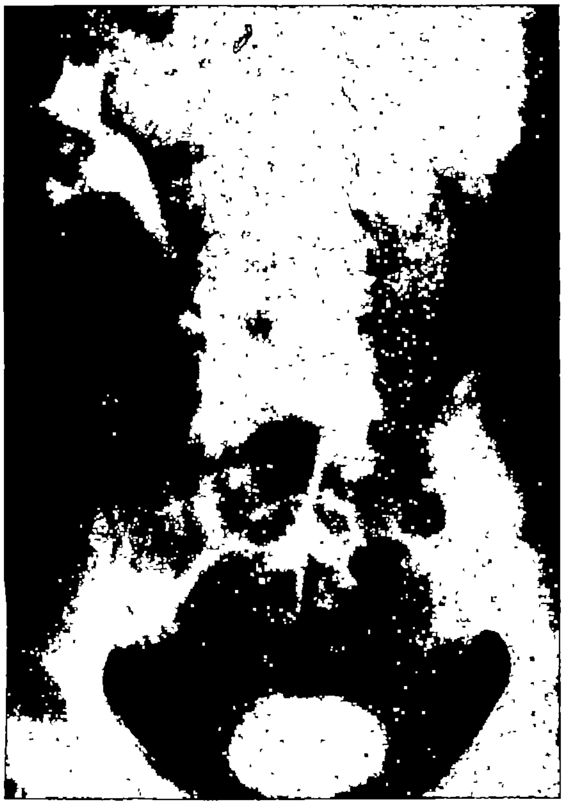

Fig.

Comment

Bromocriptine is an ergot alkaloid related to methysergide, itself a known cause of RPF. With the recent success of high dose bromocriptine therapy in the management of Parkinsonism this side effect will presumably become more frequent. Testicular retraction, although an unusual presentation of RPF, should be sought.

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Ureterorectal Fistula

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Case Report

A 66-year-old woman underwent a radical hysterectomy and bilateral salpingo-oophorectomy for a well differentiated endometrial carcinoma. The operation was difficult and therefore the cervix was left behind. Post-operatively she developed dysuria and urinary incontinence *per rectum*. There was no faecal incontinence or pneumaturia.

An IVU revealed a slightly dilated left pelvicaliceal system and a fistula into the rectum from either the lower left ureter or the bladder (Fig.). There was no gas in the urinary tract. A nephrostomy was performed and an antegrade pyelogram confirmed a ureterorectal fistula. An attempt was made to insert a double-J ureteric stent via the nephrostomy and then via cystoscopy, but the lower ureter could not be negotiated. At laparotomy, the pelvis was clear of tumour and the ureter was easily freed from the anterior surface of the rectum A cystotomy was made and the ureter reimplanted with the help of a psoas hitch A temporary double-J stent was inserted.

Comment

Ureterocolic fistulae are uncommon and ureterorectal fistulae are extremely rare. Presentation is with

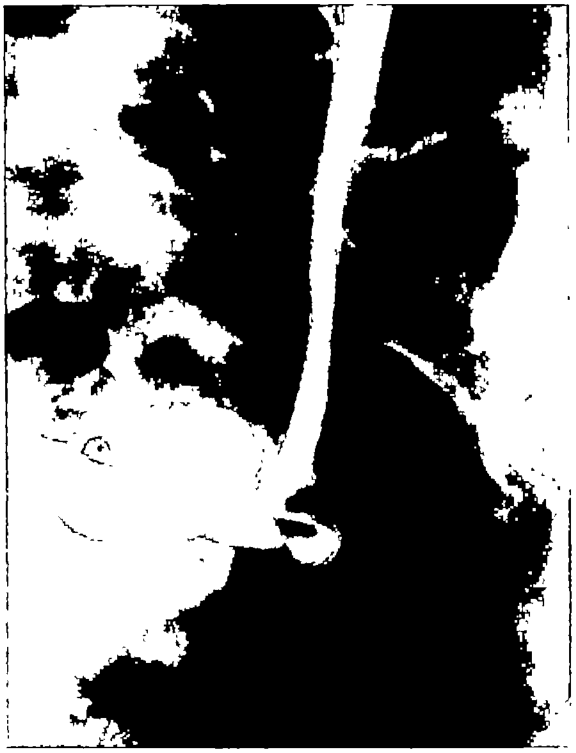

Fig.

faecaluria, pneumaturia, urinary tract infection and watery diarrhoea (Heney and Crooks, 1984). Prior to 1925, tuberculosis was the commonest cause of ureterocolic fistula; more recently, Crohn's disease, diverticular disease, carcinoma, radiotherapy and trauma (including surgical) are more usually implicated (Krishna *et al.*, 1977). Following radical hysterectomy, factors leading to ureteric fistulae include recurrent carcinoma, radiotherapy, infection and ureteric devascularisation (Roberts *et al.*, 1985).

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Bladder Outflow Obstruction Secondary to Intravenous Amphetamine Abuse

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Case Report

A 32-year-old male presented with a 2-day history of frank haematuria, dysuria and suprapubic pain. This had been preceded for several months by symptoms of bladder outflow obstruction, including marked hesitancy, poor stream and a feeling of incomplete voiding. He admitted to regular intravenous amphetamine abuse of up to 7 g/day since 1984. His generally unco-operative behaviour also demonstrated signs of mental depression and fatigue. Repeated blood pressure recordings revealed a diastolic pressure of between 110 and 150 mmHg. On examination of his abdomen there was an enlarged, tender bladder up to the level of the umbilicus. There was no evidence of any neurological deficit. Investigations revealed a plasma urea of 21 mmol/l, creatinine 269 μmol/l and creatinine clearance 12 ml/min. His white blood count was elevated at 17.7×10^9/l and a mid-stream urine culture grew $> 100{,}000$ cols/ml of coliform bacilli sensitive to ampicillin. An intravenous urogram demonstrated poor contrast excretion and bilateral hydronephrosis with a large, thick-walled bladder (Fig.) which failed to empty significantly on micturition. Ultrasound examination confirmed gross hydronephrosis and a large residual following micturition. Cystourethroscopy revealed no evidence of mechanical obstruction, with an acute, haemorrhagic cystitis and a residual volume >1 litre of foul-smelling, purulent urine.

Urinary flow studies demonstrated a maximum flow rate of 12 ml/s for a voided volume of 372 ml. Urodynamic evaluation revealed an unstable, low compliance bladder with a capacity of 1057 ml. Above a filled volume of 350 ml, the detrusor pressure was consistently above 50 cm H_2O. Voiding was obstructed with a peak flow of 15 ml/s from an unsustained detrusor contraction of 130 cm H_2O. The voided volume was 805 ml. Videocystourethrography showed incomplete opening of the bladder neck and proximal urethra during voiding. Oral ampicillin and prazosin were commenced, combined with bladder washouts and intermittent self-catheterisation. The patient has, however, repeatedly failed to attend for follow-up.

Comment

The high-pressure, urinary retention demonstrated in this case probably occurred secondary to an amphetamine-induced functional obstruction at the level of the bladder neck and proximal urethra.

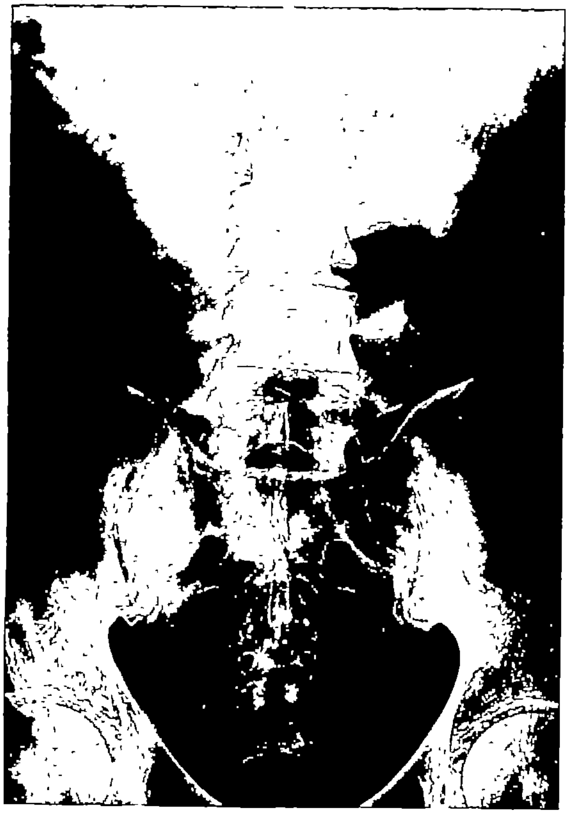

Fig. A 30-min IVU film showing poor concentration of contrast and a large volume thick-walled bladder.

However, the findings may also, in part, represent a direct effect of amphetamines on the bladder. The resulting voiding pattern was consistent with a hypocompliant neuropathic bladder. The peripheral, alpha-sympathomimetic effects of amphetamines on the urinary bladder are well known, this pharmacological action having been used in the treatment of enuresis (Innes and Nickerson, 1975). A previous report suggested that this action produced such powerful bladder neck contractions that, in the case presented, it resulted in rupture of the bladder (Bennett and Delrio, 1980). Prazosin, a selective alpha-1 adrenoreceptor antagonist, has been shown to improve urinary flow, probably by relaxing the bladder neck and prostatic urethra, in patients with benign prostatic hypertrophy (Kirby *et al.*, 1987). This, therefore, appeared to be the long-term treatment of choice in this patient, particularly in view of the associated hypertension. Until an objective response could be established the voiding difficulties were temporised using intermittent self-catheterisation. Unfortunately, however, due to poor patient compliance the long-term results are not available.

References

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Innes, I. R. and Nickerson, M. (1975). Norepinephrine, epinephrine and the sympathomimetic amines. In *The Pharmacological Basis of Therapeutics*, ed. Goodman, L. S. and Gilman, A Fifth edition Chapter 24, pp. 477–513. New York: Macmillan.

Kirby, R. S., Coppinger, S. W. C., Corcoran, M. O. *et al.* (1987) Prazosin in the treatment of prostatic obstruction A placebo-controlled study. *Br. J. Urol.*, **60**, 136–142.

Requests for reprints to: N. M Goble, Department of Urology, Bristol Royal Infirmary, Bristol BS2 8HW.

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Points of Technique

Sclerotherapy with Tetracycline for Hydrocele of the Tunica Vaginalis Testis

X DING, *People's Hospital, Chaohu, Anhui, China*

It has been reported that tetracycline, being both antibacterial and sclerosing, is an ideal agent for the treatment of hydrocele of the tunica vaginalis testis (Bødker *et al.*, 1985).

A study was made of 20 patients (average age 44 years, range 3–71) seen over a 2-year period. All had a unilateral hydrocele with no hernia or other scrotal disease. The average duration of the hydrocele was 14 years (range 1–50).

The average volume of fluid aspirated from the hydrocele was 343 ml (range 25–1200). The aspirated fluid was straw-coloured in 19 cases and chylous in 1. The patients were given a spermatic cord block at the superficial inguinal ring with 1% lignocaine and the scrotal wall overlying the hydrocele was then infiltrated. The hydrocele was punctured with a 12 gauge needle and after the fluid was evacuated, 500 mg tetracycline diluted in 5 ml isotonic saline were injected. The patients were re-examined 6, 8 and 14 months after treatment.

In 8 patients a recurrent hydrocele developed on the same side within 2 months of treatment and in 2 patients a recurrence developed within 6 months. The remainder were cured after the first procedure. The size of the recurrent hydrocele was markedly less than before treatment. There were no haematomas.

Local irritation resulting from the low pH of tetracycline may cause scrotal pain spreading from the spermatic cord to the waist and even to the perineum. We gave the patients a spermatic cord block before treatment and only 1 complained of pain along the spermatic cord. In 6 cases 1% lignocaine was used as solvent instead of isotonic saline, its pH being 3.5 to 5.5 (between tetracycline and isotonic saline).

Reference

Bødker, A., Sommer, W., Andersen, J. T. *et al.* (1985) Treatment of hydrocele of the testis with aspiration and injection of tetracycline. *Br J Urol*, **57**, 192–193

Requests for reprints to: X. Ding, Chaohu People's Hospital, Chaohu, Anhui Province, China

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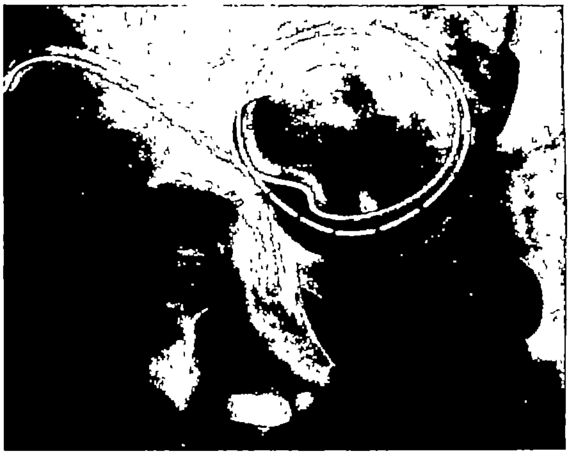
Expulsion of Urethral Calculus following Intermittent Closure of Suprapubic Catheter

M. N. MHIRI, H. KRICHEN and M. L. SMIDA, *Department of Urology, Hedi Chaker Hospital, Sfax, Tunisia*

We have found that temporary suprapubic puncture, used primarily to relieve acute retention caused by an impacted urethral calculus, may lead to spontaneous expulsion of the stone.

Spontaneous passage of the calculus after bladder puncture has been reported by Amin (1973). We have used the method in 42 males (23 boys and 19 adults) with impacted urethral calculi (Fig.). It was successful in 27 cases (boys 66%; adults 63%); 77% of the stones which were expelled were located in the anterior urethra; large oxalic stones usually failed to pass and were removed surgically. When the method was successful, 80% of the calculi took less than 3 days to be ejected.

We recommend leaving the suprapubic catheter in place for 2 to 4 days in order to allay oedema and sphincteric spasm. The tube is then closed and the patient asked to void; the stone may move downwards until its ejection via the urinary meatus. This innocuous method avoids surgery and endoscopic manoeuvres which could harm the urethra, especially in children.



Reference

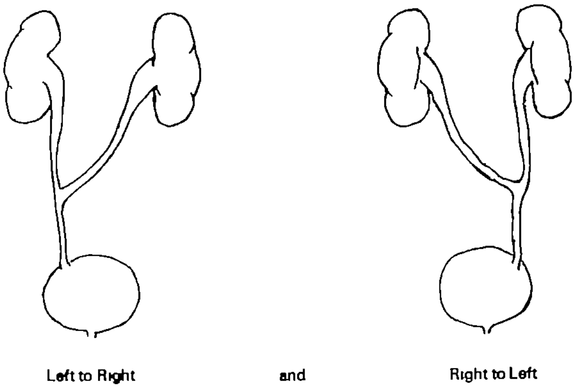
Amin, H. A. (1973) Urethral calculi. *Br. J. Urol.*, **45**, 192–199.

Requests for reprints to: M. N. Mhiri, Department of Urology, Hedi Chaker Hospital, 3000 Sfax, Tunisia.

Transuretero-ureterostomy (Squared): Left to Right and Right to Left in the Same Patient

D. CRANSTON, *Department of Urology, Churchill Hospital, Oxford*

Mr R.H., aged 64 in 1978, presented with haematuria. An IVU showed left hydronephrosis and a dilated upper left ureter which was compressed as it passed between two large bladder diverticula. Cystoscopy showed tumour in one of the diverticula and he subsequently underwent a partial cystectomy and diverticulectomy, and a left to right transuretero-ureterostomy. Small recurrences were easily controlled. In 1985 he complained of increasing symptoms of bladder outflow obstruction and underwent a transurethral prostatectomy. Histology showed poorly differentiated adenocarcinoma but a negative bone scan and he received a course of radical radiotherapy. Early in 1986 he developed lymphoedema of the right leg due to disease progression and was started on anti-androgens. Later that year he became anuric as a result of prostatic tumour obstructing the lower right ureter. After discussion with the patient a laparotomy was performed. The left ureter had become distended and elongated due to the obstruction and was now long enough to be reimplanted into the bladder, and a right to left uretero-ureterostomy was performed (Fig.) The patient recovered well with resolution of his renal failure, although he died 6 months later from his disease.



Transuretero-ureterostomy

This curious sequence of events seems to be unique in the world literature.

Requests for reprints to: D. Cranston, Department of Urology, Churchill Hospital, Headington, Oxford OX3 7LJ.

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0007-1331/89/0064-0324/$10 00

Correspondence

Dear Sir,

re **Adenine phosphoribosyltransferase deficiency: 2,8-dihydroxyadenine urolithiasis in a 48-year-old woman.** J.-P. Usenius *et al. Br. J. Urol.*, **62**, 521–524, 1988.

The above article adds one further case report to the world literature on this rare but interesting disorder. Of particular interest was the fact that urolithiasis occurred in an adult female patient. H. A. Simmonds (*Clin. Chim. Acta*, **160**, 103–108, 1986) reported that 70% of cases are diagnosed in males and approximately 70% occur in children.

The recommendation that APRT deficiency should be considered in patients with radiolucent renal calculi and normal serum urate levels implies that uric acid calculi are usually found in association with hyperuricaemia. In fact, three-quarters of uric acid stone formers have normal plasma urate levels (G. A. Rose. 1982. Other metabolic causes of stones. In *Urinary Stones. Clinical and Laboratory Aspects.* P. 240. Lancaster: MTP Press) and only 20% of patients with primary gout and 40% of patients with secondary gout develop uric acid nephrolithiasis (T. F. Yu and A. B. Gutman. *Ann. Intern. Med.*, **67**, 1133–1148, 1967).

On the basis that a pre-operative diagnosis was made, surely the fragility of 2,8-hydroxyadenine (DHA) calculi would make them amenable to treatment with extracorporeal shockwave lithotripsy rather than endoscopically if situated in the kidney or proximal ureter.

Although it seems rational to monitor the response to allopurinol by confirming the absence of dihydroxyadenine in the urine, I am unsure as to how accurate this is since the reported patient developed a calculus, although urine analysis was normal.

Yours sincerely,

M. J. Gleeson
Scott Department of Urology, Baylor College of Medicine, Texas Medical Center, Houston, Texas 77030, USA.

Reply by J.-P. Usenuis. I would like to thank Dr Gleeson for his comments on our case report. Our main concern is to prevent urinary stones in this situation on the basis of their pathophysiology. It should be possible to find a sensitive method to monitor patients' response to allopurinol and diet therapy. At the moment we examine the urine for crystals but suggest that high performance liquid chromatography might be suitable.

In the absence of a lithotriptor in our hospital we are unable to comment on the value of extracorporeal shockwave lithotripsy for these calculi but in view of the structure of 2,8-dihydroxyadenine stones we consider that they are suitable for treatment by endoscopic irrigation.

Dear Sir,

re **TNM Classification of Genitourinary Tumours 1987—Position of the EORTC Genitourinary Group.** F. H. Schröder *et al. Br. J. Urol.*, **62**, 502–510, 1988.

We, as co-editors of the TNM Classification, were sorry to read of its categorical rejection by the EORTC Genitourinary Group. We wish to comment on their report because it contains a number of misinterpretations.

1. Identical UICC and AJCC TNM. The EORTC Group was "astonished at the virtual identity" between the proposals for TNM classification by the International Union against Cancer (UICC) and the American Joint Committee on Cancer (AJCC). The identity of the two classifications was indeed intentional (UICC (Union Internationale contre le Cancer) (1987). *TNM Classification of Malignant Tumours.* Fourth edition. Berlin: Springer-Verlag. Pp. 2–3) and the main purpose of the revision was to eliminate the differences at all body sites between these two versions of TNM based on the principle that there should be only one international standard called TNM.

2. Definition of pT and pN categories. The new definitions of these categories were considered an improvement since they added specificity. The phrase "adequate to evaluate the highest pT category" does not necessarily mean pT4. For example, the pT for breast tumours can be made with less than a radical mastectomy as long as the primary tumour is completely removed with a margin of grossly normal tissue (UICC, 1987, pp. 96–97). A low axillary lymph node dissection may be sufficient for a pNO if the nodes are negative for tumour (UICC, 1987, p. 97). In the colon, an endoscopic polypectomy of a superficially invasive carcinoma with a stalk free of tumour is classified as pT1. This definition did *not* replace the earlier definition (UICC (Union Internationale contre le Cancer) (1978). *TNM Classification of Malignant Tumours*. Third edition. Geneva: International Union against Cancer. P. 9), as stated by Schröder *et al.*, but merely modified it to add more detail.

3. *Minimal requirements.* The change from "minimal requirements" to "procedures for assessment" reflects the growing impact today of medical-legal liability problems. The terms have changed but the meaning is the same. The general description of imaging methods was meant to be broad enough to cover the rapidly expanding techniques available to radiologists.

4. *Stage grouping.* The description of stages for genitourinary tumours was intended to bring this system into conformity with the classifications of all of the other body sites in the TNM. Cases can still be reported according to their individual T, N and M without grouping into stages if deemed appropriate.

5. *Additional descriptors.* The R category (residual tumour) is optional (UICC, 1987, p. 10). The "c" symbol was introduced parenthetically for those who wish to separate TNM from pTNM and it too is optional (UICC, 1987, p. 5). The V category (venous) was eliminated as a separate symbol so that venous invasion could be introduced to those T categories where it was relevant, *e.g.* it determines T3 of the kidney classification (UICC, 1987, p. 136).

The 1987 Classification was the combined effort of all national TNM Committees: American, British, Canadian, French, German, Italian, Japanese, Russian and South American, and the revision proposals were approved by all of these groups.

For more details we refer the reader to our description of the 1987 revision of the TNM giving background information and a comparison of the new and old editions (*Cancer*, **61**, 2310–2314, 1988) as well as to a recent letter to the Lancet (II, 1945, 1988) which addressed criticism of the urological classification (*Lancet*, **II**, 1145–1146, 1988).

Before they reject the classification out of hand we urge the EORTC Genitourinary Group to test the new TNM Classification in their clinical trials against the previous classification (or any others that are relevant). This could provide data upon which the next revision is based.

Finally, we find it shortsighted of the Editorial Committee of the British Journal of Urology to "publish articles based on the third edition of the Classification only" (*Br. J. Urol.*, **62**, 501, 1988). The professional concern for possible confusion between the two editions can be avoided by using bibliographic citations. How can the readers fairly judge the validity of the classification if it is suppressed? We hope the Editorial Committee will reconsider this decision.

Yours sincerely,

L. H. Sobin
Armed Forces Institute of Pathology, Washington, DC 20304, USA.

P. Hermanek
Department of Surgical Pathology, University of Erlangen-Nurnberg, 8520 Erlangen, West Germany.

Reply by F. H. Schröder et al. With this short statement the members of the TNM Committee of the EORTC Genitourinary Group and the co-authors of the Group's paper would like to react on behalf of the EORTC GU Group concerning the letter by Drs L. H. Sobin and P. Hermanek.

The EORTC GU Group appreciates the reaction of Drs Sobin and Hermanek. Their comments have been read and considered very carefully. The record of our Group shows that we have spent considerable effort on international collaboration and TNM support. In spite of the fact that there remain differences of opinion, the Group will continue to work in this direction and hopes for a correction of the obvious mistakes in urological tumour classification at the earliest convenience of the UICC.

Further repetition of arguments serves no purpose. In spite of our criticism, the Genitourinary Group of the EORTC greatly appreciates the positive aspects of the TNM system and the efforts of both editors of the UICC booklet to co-ordinate all different national proposals into one balanced end result. The Group will take steps in the near future to promote international consensus on better definitions of TNM categories. The Group agrees with the suggestion that the new system be tested in large clinical trials wherever possible and suitable.

Reply by Editorial Committee. The Editorial Committee of this Journal discussed the letter from Drs Sobin and Hermanek and concluded that our acceptance of the detailed criticisms of the 1987 classification does not amount to "out of hand" rejection. We would remind Drs Sobin and Hermanek that the onus was on them to demonstrate the need for change rather than to make changes that now need validation.

British Journal of Urology (1989), 64, 326–327

Notices

British Association of Urological Surgeons
President: R. T. Turner-Warwick, DSc, DM, MCh, FRCP, FRCS, FACS

Annual Meeting. Scarborough. 10–13 July 1990

Abstracts of contributions to be considered as either papers, posters or videos by the Programme Sub-Committee of Council should be submitted on the special forms available from the BAUS Secretariat. Completed forms, which should state clearly whether the submission is a paper, a poster or a video, must be returned to the Honorary Secretary by Friday, 5 January 1990.

Abstracts not on the special forms will NOT be considered.

All correspondence to: M. G. Royle, FRCS, Honorary Secretary, British Association of Urological Surgeons, Royal College of Surgeons, Lincoln's Inn Fields, London WC2A 3PN.

British Association of Urological Surgeons
President: R. T. Turner-Warwick, DSc, DM, MCh, FRCP, FRCS, FACS

Autumn Meeting: Churchill College, Cambridge. 29 and 30 September 1989

The Day Meeting of the Association on 30 September will be preceded by a Postgraduate Teaching Afternoon on 29 September, when the topic will be "Pre- and Post-natal Diagnosis and Management of Urinary Anomalies".

Further information from: R. H. Whitaker, Department of Urology, Addenbrooke's Hospital, Hills Road, Cambridge CB2 2QQ.

C.-E. Alken Prize

An endowment fund has been established to further clinical work and research in the field of Urology by presenting an annual award of SwF 10,000 for outstanding scientific endeavours. The award will be for an unpublished work in the field of Urology. An award certificate will also be presented. The prize money may be divided among several contributors.

The papers may be written in either German or English and three copies must be submitted by 30 September 1989 to: Stiftungsrat C.-E. Alken-Stiftung, Advokaturbüro Dr F. Kellerhals, Bundesplatz 4, CH-3011 Bern, Switzerland.

Each submission must be affixed with a code word and must not bear the author's name. In addition, a sealed envelope labelled with the code word is to be included, containing on a separate sheet of paper the author's name and professional standing, together with the code word.

The adjudicators for the award will be the Board of Directors of the endowment fund and their decision will be final.

The Surgitek Prize

The Prize consists of a fully sponsored visit to the American Urological Association Annual Five-day Meeting, together with a tour of Surgitek's manufacturing facility in Racine, Wisconsin. It is open to trainees in urology and consultants who are within 5 years of first appointment. Entrants should submit a written paper, which may be on any subject, but must be unpublished, and must not have been submitted previously for the Surgitek Prize, or other prizes. The winning entry will be the one which is considered to be "The most significant contribution to urology".

Entries will be judged by three members of BAUS Council nominated at the October meeting of Council. Papers should be submitted in triplicate to the Honorary Secretary by 1 January each year.

Hans Marberger Prize

The Hans Marberger Prize will be awarded for the first time at the meeting of the German Urological Association in Hamburg in 1990. The prize, which will be donated by Karl Storz Ltd, will amount to öS 50,000 and will be awarded biennially for the best paper in the field of reconstructive surgery in urology or endourology. The award may be split.

Papers may be written in either German or English and should be submitted in triplicate to Dr H. Fuchshuber, Adamgasse 15, A-6020 Innsbruck, by 1 March 1990.

A code word should be affixed to each manuscript, which should not bear the author's name. In a separate envelope bearing the code word the following information should be given: author's first name, surname, position, and code word.

West Midlands Urological Research Group: Seminar on Surgical Management of Penile Disorders

Birmingham. 6 October 1989

Further information from: Department of Urology, Queen Elizabeth Hospital, Edgbaston, Birmingham B15 2TH.

Early Prostatic Cancer—Which Treatment?

Newport, Gwent, 3 November 1989

Further information from: Mr W. B. Peeling, Department of Urology, St Woolos Hospital, Newport, Gwent NP9 4SZ.

Annual Meeting of the British Andrology Society

Edinburgh. 10 and 11 November 1989

Further information from: Dr C. Barrett, Department of Obstetrics and Gynaecology, University of Sheffield Medical School, Beech Hill Road, Sheffield S10 2RX, or Mr T. B. Hargreave, Department of Surgery (Urology), Western General Hospital, Edinburgh EH4 2XU.

Annual Meeting of the Swiss Society of Urology

Aarau, Switzerland. 21–23 September 1989

The main themes will be Renal Carcinoma and Ultrasound in Urology.

Further information from: Professor R. Tscholl, Urologische Klinik, Kantonsspital, CH-5001 Aarau, Switzerland, or Professor D. Hauri, Urologische Klinik, Universitätsspital, CH-8091 Zürich, Switzerland.

Fourth Steglitz Pediatric Surgical Symposium: Laser Application in Children

Berlin, West Germany. 10 and 11 November 1989

Further information from: Dr Felix Schier, Department of Pediatric Surgery, Free University of Berlin, Hindenburgdamm 30, 1000 Berlin 45, West Germany.

18th Biennial Congress of the Urological Association of South Africa

Durban, South Africa. 22–26 April 1990

Topics: Genitourinary Cancer, Urolithiasis, Urologic Injuries, Paediatric Urology, Advances in Urology and Andrology.

Pre- and post-Congress safaris.

Further information from: Uro 1990, P.O. Box 17008, Durban 4013, South Africa.